SEPTEMBER 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

PETER VOGEL

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NEW YORK PATHOLOGICAL SOCIETY

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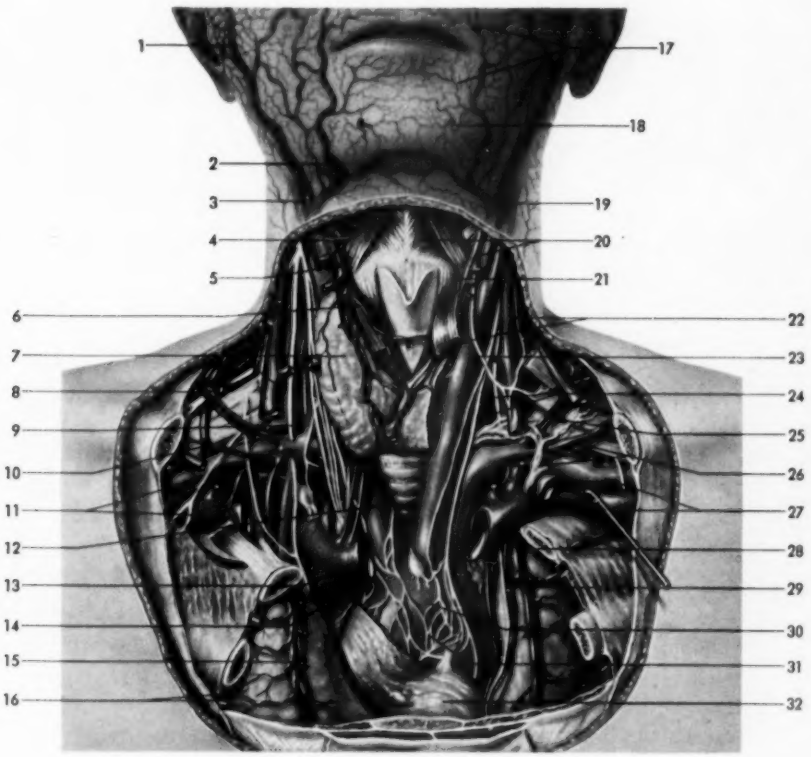

1 Superficial temporal artery
2 External maxillary artery
3 Internal carotid artery
4 Superior laryngeal artery
5 Right superior thyroid artery and vein
6 Cricothyroid branches of superior thyroid artery and vein
7 Internal jugular vein; thyroid gland
8 Right superficial cervical artery
9 Right inferior thyroid artery
10 Right suprascapular artery
11 Right subclavian artery and vein
12 Innominate artery
13 Left innominate vein
14 Superior vena cava
15 Right internal mammary artery
16 Anterior intercostal artery and vein
17 Superior and inferior labial arteries
18 Mental artery and mental foramen
19 External carotid artery
20 Mylohyoid muscle; left superior thyroid artery
21 Thyrohyoid muscle
22 Sternothyroid muscle; internal jugular vein
23 Left common carotid artery
24 Left inferior thyroid artery; vagus nerve
25 Left superficial cervical artery and vein
26 Left suprascapular artery; thoracic duct
27 Left subclavian artery and vein
28 Left internal mammary artery
29 Pericardiacophrenic artery
30 Aortic arch
31 Superficial cardiac plexus
32 Pericardium

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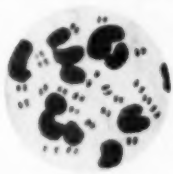

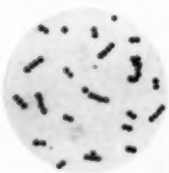

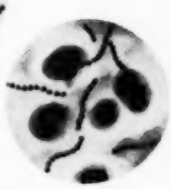

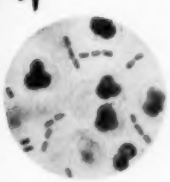

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1. Spink, W.W.: J.A.M.A. *152*:585 (June 13) 1953
2. Bush, W.L.: Southern M. J. *45*:870 (Sept.) 1952
3. Berkowitz, D.: Antibiot. &Chem. *3*:618(June)1953

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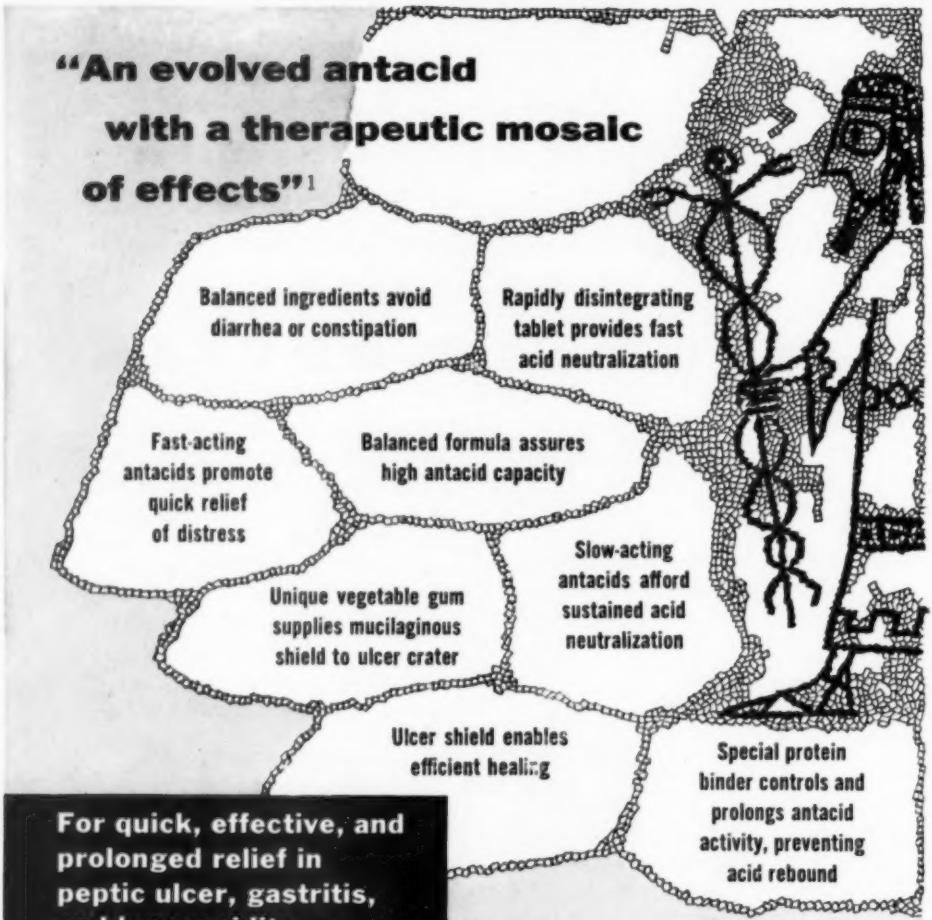
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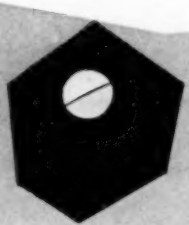

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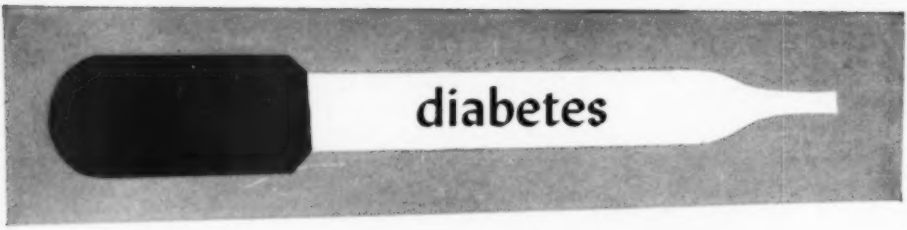

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1. Blotner, H., and Marble, A.: New England J. Med. *245*:567 (Oct. 11) 1951.
2. Steine, L.: GP *8*:45 (July) 1953.

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1. Werner, A.: Acta endocrinol. *13*:87, 1953.
2. Malleson, J.: Lancet *2*:158 (July 25) 1953.
3. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc., 1953, p. 23.

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology 3:1 (Feb.) 1952.
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SECOND SERIES SEPTEMBER 1954 VOL. 30, NO. 9

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 30, NO. 9 SEPTEMBER 1954

CURRENT PROBLEMS IN BLOOD TRANSFUSION*

PETER VOGEL

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BECAUSE of recent progress in simplifying the collection, preservation, and administration of blood, there has been a marked increase in the number of transfusions in the past two decades. However, the ready availability and ease of administration has occasionally led to abuse of this therapy.[1] Often transfusions are given with inadequate indications and without sufficient realization of the hazards or dangers that may be involved.[2] Many harmful and even fatal reactions probably occur which fail to be attributed to blood transfusion.

It has been estimated that more than four million units of blood have been utilized yearly in this country alone.[3] This increase in the number of transfusions could only have been brought about by widespread establishment of blood banks throughout the country.

The need for blood and blood fractions which became evident with World War II has resulted in rapid strides in the organization of blood

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, October 28, 1953.

banks. Advances also have been made in the methods of preservation and the techniques of blood grouping and detection of antibodies.

Certain new problems have developed as a result of the rapid development of blood banks throughout the country and the increase in the number of transfusions given. During World War II there was a considerable shortage of blood for both civilian and military requirements. The American Red Cross took care of the military needs through voluntary blood contributions, as well as of some civilian requirements.[4] In larger population centers, the difficulty of securing voluntary blood donors made the replacement of blood in hospital blood banks difficult, so that it was necessary to purchase from blood banks where paid donors were available. In smaller communities, where the spirit of cooperation is much better, the replacement of blood by hospital blood banks is on a completely voluntary basis. The important problem of how this may be accomplished in hospitals in larger cities has not been solved. There is constant competition for available donors who divide their donations among several agencies, while a large untapped segment of the population does nothing to support a program for a steady supply of blood.

Collection of Blood

Welfare of Donor: The rejection of donors on the basis of certain findings varies to some extent, depending on the center, but the main considerations are the welfare of the donor and that of the recipient. The strictness with which some of the regulations are applied depends largely on the director of the blood bank. There have been so many changes in the attitude in the past several years with regard to these requirements that the City of New York is now in the process of revising the section of the Sanitary Code relating to blood banks and transfusions.

Minimum requirements and regulations laid down by the City, State, and Federal agencies are necessary for the welfare and protection of the donor. Certain diseases such as syphilis, malaria, tuberculosis, or hepatitis prohibit donation. The screening methods used have disclosed instances of unsuspected anemia and other abnormalities, and the rejected donors have been referred to their physicians for treatment. Thus, some prospective donors have benefited by applying to blood banks. In addition, millions of individuals have been given cards with their blood group and Rh type and are available when necessary for a donation for their

relatives or friends or for any emergency in the community.

The handling of the blood donor has improved to such an extent that most individuals are no longer fearful of giving a donation. Recruitment is less of a problem today, thanks to the remarkable education of the public that has been accomplished. However, in order to have a donor continue to have confidence in the protection of his health and welfare, blood banks must use all the necessary care, attention, and courtesy in handling the candidate who wishes to donate blood. The risk of homologous serum jaundice to donors should be considered, since this can be completely avoided by using only autoclaved equipment for testing, local anesthesia, and phlebotomy.

Welfare of Recipient: Consideration must be given to the welfare of the recipient when blood is taken for the purpose of transfusion.

The transmission of most diseases is much less likely to occur with the present method of donor selection. Treponema pallidum is destroyed if blood is kept at refrigerator temperature for ninety-six hours.[5] Quarantine of the blood for this period is obligatory if the donor is not given a complete physical examination.

Malaria can be transmitted by blood transfusion.[6] Plasmodia have been known to appear in the blood years after an attack of the disease. The malaria parasite also survives in stored blood and is not destroyed by refrigeration. The risk of this disease is, of course, greatest in endemic areas. Veterans of the Armed Forces who contracted the disease will be a potential source of transmission for some time.[7] The risk of transmission is greatly reduced although not entirely eliminated if there is no history of attack for over two years.

Contaminated Blood: One of the serious problems arising in transfusion therapy is the prevention of massive contamination of blood by bacterial organisms.[8] It has been shown that as many as 2 to 5 per cent of blood bank donations may be contaminated with bacteria. Most of these bacteria do not grow readily at refrigerator temperature, but their products may lead to a marked pyrogen reaction.[9] When sedimented red cells are to be used, the plasma should be removed just prior to administration in order to prevent growth of bacteria which may be introduced by this procedure. A number of bacteria, the most important of which are the gram-negative chromogens,[10] grow readily at 4° C. and have been responsible for a number of fatal transfusion reactions.[11]

By far the greatest problem in the operation of blood banks is the

transmission by transfusion of homologous serum jaundice.[12-16] The elimination of this transmissible disease is our greatest present challenge. Certain chemicals, such as the nitrogen mustards, have been tried for the sterilization of blood and blood plasma to prevent hepatitis.[17] Early reports indicated that the virus of serum hepatitis is destroyed by ultraviolet irradiation [18,19] However, recent evidence by a number of investigators[20-22] has indicated that the virus of hepatitis can be transmitted by pooled irradiated plasma and that irradiation is not adequate. Human thrombin,[23, 24] used for hemostasis in neurosurgery, has been found to be contaminated with the virus of hepatitis. All methods of testing stored blood and the most careful screening of the donors, have not eliminated this hazard in transfusion.[25] At present this must be considered as a calculated risk in the administration of any blood or plasma, since there is no effective method of destroying the virus. Fortunately, albumin (Fraction V)[26] and gamma globulin (Fraction II) are free of virus, so that therapy with these valuable adjuncts is no problem. Unfortunately, Fraction I (fibrinogen, antihemophilic globulin) and Fraction IV may contain the virus.[27] However, homologous serum hepatitis has not been reported following the use of antihemophilic globulin as prepared by the ethyl alcohol precipitation method.[24]

Method of Collection: The standard equipment for blood collection is fairly uniform and interchangeable. Some blood banks still prefer to collect by gravity rather than by vacuum. As a substitute for glass bottles, a disposable plastic bag is available.[28] Such equipment has the advantage of relatively small bulk, little weight, no breakage, and easy storage in a refrigerator. Uncontrolled hemorrhage due to thrombocytopenia responds poorly to treatment with ordinary bank blood because the platelets are damaged under the conditions of collection and storage. Under these circumstances, where a nonwettable surface is required to preserve the platelets, plastic bags with siliconized needles are utilized for the collection of blood.[29]

Preservation of Blood: The short survival of red cells in sodium citrate solutions was a considerable handicap in the shipment of blood overseas during the early part of World War II. In addition, the inability of blood banks to utilize the blood in a short time caused marked waste throughout the country. The National Research Council in this country and the Medical Research Council in England subsequently developed effective acid glucose-citrate mixtures for the preservation of

red cells. Standard preservatives are now in use and allow storage of blood up to three weeks before administration. About 90 per cent of transfused red cells have a normal survival in the patient if the blood has not been stored more than fourteen days. But after twenty-one days of storage, about 30 per cent of the transfused red cells do not survive more than twenty-four hours in the recipient.[30]

Recent studies by Chaplin and Mollison[31] have shown that it is possible to preserve red cells for months or years. In this process the red cells are first dehydrated with glycerin and then stored at subzero temperature. Prior to transfusion the cells are rewarmed and the glycerin removed. While a large scale program for such preservation is still in the experimental stage, it is now possible to preserve by this method rare and unusual bloods for both testing and transfusion purposes.

Immunohematologic Aspects: Rapid strides have been made in the past ten years in the technique of blood grouping and Rh typing.[32] But this new knowledge has not been applied sufficiently in blood banks.

Even though potent antiserums are now available for cell grouping, there are numerous difficulties and clerical errors which make it necessary to confirm the cell grouping by means of a serum typing for both donor and recipient. In the case of Rh typing, all individuals found negative by the usual methods should have this checked by the more sensitive antiglobulin technique. This procedure is important in typing donors, since weakly reacting Rh-positive blood[33] may immunize Rh-negative recipients. If this precaution is not taken with female recipients before or during the childbearing period, it may prevent a woman from bearing a normal offspring.[34] In addition, if a weakly positive blood is transfused to an Rh-negative recipient who is already immunized to Rh antibodies, a fatal hemolytic transfusion reaction may result.

In spite of newer and more sensitive methods which have been developed for direct matching for transfusion, many hospital laboratories and blood banks have not kept abreast of these advances. The directors hesitate to use the most sensitive method until actual trouble is encountered. This hesitation may be due in part to omissions in numerous technical bulletins put out by Civilian Defense agencies who are concerned only with large scale emergency methods of collection and administration of blood.[35]

Since the usual method of saline matching is unreliable in detecting the many new blood factors which may be the cause of serious transfu-

sion reactions, it is mandatory that the most reliable method—the indirect antiglobulin test—be used to prevent such harmful effects.

In the past decade, Rh antibodies were the main cause of transfusion reactions. Since Rh-negative recipients now receive Rh-negative blood, there is no advantage in direct matching, using the donor's red cells suspended in their own serum or bovine albumin.[36] We have found this method of matching unreliable for detecting many of the newer factors responsible for serious hemolytic transfusion reactions.[37, 38] When there is any suspicion of incompatibility or after repeated transfusions, matching by the indirect antiglobulin method is mandatory.

Because of the marked increase in blood transfusions in recent years, the importance of the problem of iso-immunization has increased. Many physicians assume that simple direct matching is adequate when only homologous blood, both group and Rh, is administered. However, because of the individuality of blood, immunization to other blood factors is always possible. Theoretically, transfusion can immunize anyone to a blood factor that he lacks. Fortunately, few individuals respond readily to such antigenic stimulation. Although uncommon, these immunizations may become difficult problems leading to severe hemolytic reactions and death. From clinical experience it is known that patients with blood dyscrasias, especially hemolytic anemia, lymphoma, cancer and lupus erythematosus, who require frequent and repeated transfusions, are more prone to immunization to some of the less antigenic blood group factors. In addition, in recipients strongly immunized to one blood factor, multiple antibodies [39, 40] to other blood factors frequently develop after further transfusions. At times, the search for a compatible donor for such a recipient may tax the facilities of any blood bank.

Two examples of multiple iso-antibodies may be cited to illustrate this aspect:

1. A thirty year old hemophiliac has suffered reactions to most of the blood transfusions he received in the past four years; his serum contains anti-K, anti-S, anti-N, and anti-f, recently described by Rosenfield et al.[41] The selection of compatible bloods for this patient is now a difficult problem.

2. A random direct matching for a patient suffering from metastatic carcinoma of the kidney was found to be incompatible due to marked immunization to hr′ (c). For over three years, with careful matching, this patient was given many subsequent transfusions of compatible blood

TABLE I—HEMAGGLUTININS ENCOUNTERED AT BLOOD BANK THE MOUNT SINAI HOSPITAL, NEW YORK CITY JAN. 1, 1949 to SEPT. 1, 1953*

Antibody	*No. of Examples*
Anti-Rhô	95
" rh′	20 (all with anti-Rhô)
" rh″	33 (16 with hemolytic anemia)
" hr′	4
" rh^w	1
" K	12
" Fy^a	2
" Jk^a	1
" M	2
" N	0
" S	2
" Le^a	9
" Le^b	12
" P	6
" A_1	7
" O	5
" B_1	1
" Lu^a	1
Unidentified isoagglutinin	9
High-titer cold agglutinin	5
Incomplete panagglutinin (acquired hemolytic anemia)	18

*56,000 blood specimens examined; 42,000 blood transfusions.

without reaction. Although additional antibodies to rh″(E) rh^w (C^w), and K factors developed, the new antibodies were readily detected and identified because of the sequence in their development, and did not seriously interfere with finding compatible bloods.

Multiple iso-antibodies may occur in pregnancy. We have encountered Rh-negative women strongly immunized to the Rh factor and also immunized for Fy^a, K, or Jk^a. It is imperative, therefore, that the serum of the mother be used to match directly the donor blood for exchange transfusions in hemolytic disease of the newborn.[42]

TABLE II—NEWER ANTIBODIES RESPONSIBLE FOR HEMOLYTIC REACTIONS

Probable	*Known*	*Unknown*
Rh-Hr	Rh-Hr	P
K	K	Le^a
Fy^a	Fy^a	Le^b
M	S	"cold" M
S	M	
s		A_1
Jk^a		B_1
Fy^b		O

From January 1, 1949 to September 1, 1953 over 42,000 blood transfusions have been administered at The Mount Sinai Hospital, New York City. We have analyzed our instances of intergroup iso-immunization during this period with the result shown in Table I.

By a preliminary screening, we have detected almost all of these antibodies (Table II) prior to transfusion and have thus avoided a large number of hemolytic reactions.

In all probability, only the RhHr, K, Fy^a, M, S, s, Jk^a, and Fy^b antibodies are capable of causing hemolytic reactions, and of these only RhHr, K, Fy^a, S, and M have been proved to do so.[43-48] The P, Le^a, Le^b, "cold" M, A_1, B_1, and O antibodies are best considered as the cause of confusion in direct matching, rather than as capable of causing hemolytic transfusion reactions.

As far as is known at present, saline direct matching followed by the antiglobulin method will detect all antibodies responsible for hemolytic transfusion reactions. Agglutination in either saline or the indirect antiglobulin test denotes incompatibility of the donor red cells. Other methods of matching are in common use but none detect all human iso-antibodies which have been described (Table III).

It is not practical for a blood bank to perform routine matching which requires over an hour to complete. The demand for blood from the average bank is so great as to tax the simplest technique. For this reason, it is desirable to supplement the direct matching with a routine

TABLE III—BEHAVIOR OF HUMAN ISO-ANTIBODIES WITH VARIOUS TECHNIQUES

Antibody	*Technique*			
	Saline	*Albumin*	*Trypsin*	*Anti-globulin*
A-B	(+)	+	+	(+)
Rho-rh′-rh″-rhw-hr′-hr″	±	+	(+)	(+)
K-k	±	±	±	(+)
Fya	±	±	—	(+)
Jka	±	—	—	(+)
Lea-Leb	(+)	+	(+)	+
M-N	(+)	+	—	+
S-s	±	±	+	(+)
P	(+)	+	+	±
Lua	(+)	+	+	±

Key: (+) preferred
+ almost always positive
± may be positive or negative
— almost always negative

system of antibody study at the time that the patient's specimen is received for typing. Thus, if a blood bank receives twelve or more bloods in a morning for typing, it is not difficult to test the serums from these specimens for the presence of intragroup iso-agglutinins. Kellner and associates [49] suggested that the serum from every patient be tested against trypsin-treated[50] group O Rh_1 Rh_2 red cells so that Rh immunization can be detected in advance. Actually, any Rh-positive group O blood may be used for this purpose, with equal success. It is even better to select three to five bloods positive for all known factors. If the patient's serum is tested against a mixture of group O cells in saline, numerous examples of "natural" iso-agglutinins, including Le^a, Le^b, O, M, and P can be detected. These antibodies are thus defined before they can cause needless confusion during matching. When necessary, further incubation at 37 °C. allows for conversion to the indirect antiglobulin test, and a more complete screening for iso-immunization.

When a blood bank is given the information that a patient has received previous blood transfusions, or that the patient has any other history suggesting iso-immunization, direct matching by the indirect antiglobulin test should always be performed. When chill, temperature rise, or any suspicion of reaction is reported following transfusion, direct matching should always be rechecked by the indirect antiglobulin technique.[51] For this purpose, a pretransfusion sample of the patient's blood should always be kept and directly matched with a suspension of the blood administered.

There are special problems which arise in blood group immunology that require the attention of an experienced hematologist. For example, an Rh-negative patient with acquired hemolytic anemia may cause considerable difficulty in typing and direct matching.

Occasionally, one encounters a patient who has been transfused and in whose blood specimen donor blood is detected making the identification of the true blood group difficult. Recently, Dunsford, et al.[52] described a rare finding in a female patient who was one of twins. Her red cells revealed two different blood groups; one genetic set of her own, the other produced by embryonic rests which remained as a result of vascular anastomosis in utero with her twin brother. Such an occurrence is not unusual in cattle, but this is the first time it has been described in man.

The use of group O Rh-negative blood in emergencies, may also cause difficulty and is not without danger.[53] Rh-negative blood is limited in supply and should be used only for Rh-negative patients, and for hemolytic disease of the newborn. The use of low titer group O blood for emergency military needs has been reported to be free of danger. However, indiscriminate use of Group O donors has led to some difficulties.[54,55] If the plasma is withdrawn before administration, this danger is eliminated.

Transfusions of type O blood with a plasma that contains a high titer of anti-A or anti-B antibodies have been shown to produce an unmistakable hemolytic reaction. Even when such universal donors are screened and A and B substance added, the incomplete form of anti-A and anti-B antibody may not be neutralized.[56] Such an incompatibility may immediately destroy some of the red cells of the patient, with a resulting hemolytic reaction, or there may be gradual loss of these cells until the transfused antibody is eliminated.

Administration of Blood

Administration of blood by the gravity method, using a large bore needle inserted into the vein will usually suffice in most cases with severe hemorrhage. Rapid transfusion,[57] by pumping air under pressure, is occasionally necessary to combat shock and severe hemorrhage effectively, but accidental death from air embolism may result unless a qualified individual is in attendance to control such a procedure. The use of intra-arterial blood transfusion in the therapy of deep shock from hemorrhage has increased in recent years.[58-60] Those favoring this method[61] feel that the intra-arterial route raises the blood pressure more quickly and effectively. Recent studies by Case et al.[62] do not substantiate these claims; controlled experiments with dogs showed that rapid intravenous transfusions were just as effective as the intra-arterial transfusions, wher given at the same rate, to control hemorrhagic hypotension.

At the present writing, the theoretical advantages of the intra-arterial method, whether by peripheral artery, intra-aortic, or cardiac routes, have not been proved.[63] Since the use of a peripheral artery may lead to gangrene of the limb,[64] such transfusions should only be attempted by an experienced transfusionist in certain cases of extreme emergency.

As a result of obesity, edema, extensive burns, or circulatory collapse, the superficial veins may not be accessible and the intra-osseous route may be employed.[65, 66] Usually, positive pressure is necessary for the administration of the blood. In certain emergencies, this route may be lifesaving, but the hazard of secondary osteomyelitis, embolism, and perforation through the bone, especially in infants and children, make this a dangerous method of administration.

The fontanel is now rarely used for administering blood or plasma to infants because of the danger of thrombosis of the sagittal sinus.

Exchange transfusion, by way of the umbilical vein,[67] for hemolytic disease of the newborn is an outstanding technical advance in the treatment of this condition.

The newer methods of cross transfusion[68] in severe uremia should be mentioned. Such transfusions may exchange as much as 25 to 50 l. of blood in a period of several hours. At present, this method is not without considerable risk to both patient and donor and should be considered as in an early experimental stage.

Use of Whole Blood or Substitutes: While it is not the purpose in

this presentation to discuss the indications for blood therapy, it is necessary to point out the present opinion concerning the use of "blood substitutes." There is no true substitute for whole blood. It is the most effective substance to combat shock due to hemorrhage. If whole blood is not readily available, certain substances may be used in an emergency. A number of these substitutes are now commercially available and are called plasma volume expanders or extenders. Numerous investigators have reported the advantage or efficacy of one product over another, but not one of the expanders has entirely fulfilled the theoretical requirements.[69] When the plasma expanders were first available, most authors reported promising results in their use; but the accumulated evidence thus far is less convincing, and in civilian practice, at least, there is no tendency to resort to these substitutes. Globin derived from red cells has some promise as a blood expander, although the material in its present form is still not suitable for use.[70]

Albumin,[71] a blood derivative which does not transmit the virus of hepatitis, could be used effectively as a plasma expander if sufficient supplies were available.

Modified protein, such as gelatin, oxypolygelatin, and polyvinylpyrrolidone (PVP), have been used for some time, but the effectiveness in shock due to hemorrhage is not impressive.

Dextran[72] has been given the widest trial in this country and abroad. The high percentage of allergic reactions would limit the widespread use of this product.[73] The single advantage that all of the expanders have over plasma is that they do not transmit the virus of hepatitis.

Until more experience is gained, it would be wiser to limit the amount of these substitutes to 2000 cc. or less.

The use of red cells[74] to combat anemia and as a source of protein has recently been suggested. This method may require large volumes to elevate the total protein and the hazard of circulatory overloading must be considered. In nearly all types of anemia the use of sedimented red cells is preferable.[75-77] In patients with heart disease,[78] for whom a large volume is contraindicated and sodium is restricted, it is the only method without danger. In premature and some older infants, to whom blood is given by syringe, the use of packed or sedimented cells permits a smaller amount of injection and prevents the danger of overloading.

Hemolytic Transfusion Reactions: The increased use of blood therapy in the past fifteen years has led to an increase in the number of

transfusion reactions, but the proportion is smaller than was previously encountered. Hemolytic transfusion reactions are still the most serious, because of the danger of death. The technique of pretransfusion screening, discussed earlier should be followed to prevent such reactions whenever possible. Improper storage and handling of the donor's cells is an occasional source of trouble giving rise to undue hemolysis of blood. In hemolytic transfusion reactions, the reason for the incompatibility should be found as soon as possible, so that appropriate steps may be taken to counteract the effects. If the reaction is due to incompatibility of the main blood groups, and 300 cc. or more of blood have been given, the condition may become critical and recovery may be in the balance for a number of days.

During the stage of anuria, while the kidney is unable to excrete water, fluids should be limited to prevent overloading. If the cause of the incompatibility is immediately ascertained, a compatible transfusion may be given. The patient should be kept in fluid and electrolyte balance during the critical period of oliguria and during the recovery stage.

If the cause of the hemolytic reaction is not immediately certain, no further blood should be administered unless a pretransfusion sample is available for direct matching by the antiglobulin technique. A post-transfusion sample taken at this time may be compatible because the antibodies have been neutralized or absorbed by the recent transfusion (the so-called negative phase) and several days may elapse before the agglutinins are again demonstrable.

Pyrogens are the most common cause of reactions. They are characterized by chills and fever occurring during a transfusion or shortly thereafter. The reaction may be mild or a severe chill with a temperature rise to 105°F. The temperature usually returns to normal after several hours. Even with the most meticulous care, pyrogen reactions cannot be entirely avoided in some patients. However, the use of reliable, disposable collection and administration equipment has markedly reduced the number of reactions for which pyrogens are believed responsible.

Circulatory Overload: Clinically, circulatory overload can be a serious complication. The onset of symptoms may occur during or shortly after transfusion, with sudden dyspnea, orthopnea, cyanosis, cough, and physical signs of pulmonary edema. Older people and those with heart disease are especially susceptible, and caution should be

exercised in this group. Infants and young children may suffer circulatory overload, especially if large amounts of blood are injected rapidly into the veins.

Allergic Reactions: About 1 to 5 per cent of blood transfusions are followed by reactions of an allergic type. The reactions are seldom serious and consist usually of urticaria, occasionally of angioneurotic edema, and, more rarely, of asthma. However, the last-mentioned, in a very ill patient, may be fatal unless the transfusion is immediately discontinued and small doses of adrenalin are administered. Many such serious reactions may now be decreased or prevented by the addition of 25 mg. of Pyribenzamine[79] or 10 mg. of Chlor-Trimeton[80] to the blood in the bottle before administration. Also, use of antihistamines[81] in this manner often depresses the chill and fever which is experienced by many patients following the routine administration of blood. Such febrile reactions are common in patients who suffer from ulcerative colitis, bleeding peptic ulcer, some blood dyscrasias, and cancer.

It is believed that the sensitivity which develops in certain patients to some component of the donor's plasma can be prevented by the use of washed cells.[82, 83]

Exogenous Hemochromatosis: The association of hemochromatosis with multiple transfusions has been recognized for some time, but it is only recently that this complication has been observed with increased frequency. Because the body lacks a mechanism for eliminating the excess iron, in a number of patients with chronic aplastic anemia, chronic hemolytic anemia, and Cooley's anemia, who require frequent transfusions over a period of years, iron is deposited in the tissues. As a consequence of the iron overload, changes take place in the various organs, especially the liver and pancreas, resulting in the syndrome of hemochromatosis.[84]

Summary and Conclusions

In this discussion only the highlights of the current problems in blood transfusion have been mentioned. The transmission of homologous serum jaundice remains the greatest challenge in blood therapy. A more widespread application of the newer advances in blood group immunology may markedly reduce the number of hemolytic transfusion reactions.

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MODIFICATION OF RADIATION INJURY*

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THE radiation syndrome that is characteristic of mammals that have been exposed to midlethal (LD_{50}) or lethal (LD_{100}) amounts of x-rays, gamma rays, or fast neutrons has been described by many clinicians and radiobiologists.[1-7] As a result of these observations, much attention is being directed toward finding means of altering radiosensitivity, from the cellular to organismal levels. Efforts to change the radiosensitivity of the mammalian organism or a specific tissue of its body are largely concentrated upon the administration of chemicals or biologicals, or the initiation of other measures prior to, during, or after irradiation of the organism. Estrogen,[8] cysteine,[9] and glutathione[10] markedly enhance the survival of rats and mice when given prior to the administration of whole-body x-radiation in the lethal range. Cysteinamine[11, 12] has been found to have an even more strikingly beneficial effect than cysteine.

Likewise, survival is enhanced if, during exposure to lethal dosages of x-radiation, the animals are subjected to severe oxygen deprivation[13] or cyanide intoxication.[14]

Neither the pre-irradiation measures nor those instituted during irradiation, as described briefly above, have any beneficial effect, using survival as the criterion, if instituted after the animals have been subjected to lethal whole-body irradiation.

Patt[15] has written a comprehensive review covering the literature on the in vivo and in vitro biochemical and physiologic effects and has summarized current concepts of the mechanism of action of ionizing radiations.

This paper is limited for the most part to a report on measures that,

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when initiated after exposure of the mammal to an LD_{100}, have a remarkable effect on survival and on recovery of the blood-forming tissue. A review of our investigations in this field has already been published.[16] Only a few of these studies are summarized here, more or less chronologically, in an attempt to show how each investigation led to another, and to emphasize certain interesting but as yet undeveloped observations.

Three possible explanations for the success of our techniques evolved quite early in the course of our studies. These are: 1) the neutralization of a toxin produced by irradiation; 2) the cellular seeding of depleted irradiated tissue; or 3) a humoral factor or factors produced and supplied by cells to the irradiated tissue. Thus, many of the experiments described below were attempts to assay the relative importance of these possibilities. Other experiments, however, were undertaken to learn more of the basic problem of blood formation without any relation to radiation injury.

The Effect of Splenectomy on the Toxicity of Sr(89-90)

Interest in the spleen as an important locus of erythropoiesis developed during some experiments on the effects of radiostrontium in mice.* Animals that were given Sr(89-90) (2.0 uc/g) did not develop anemia although their bone marrow became completely aplastic within a few days after injection and remained so for more than a month. The lymph nodes became moderately active centers of hematopoiesis, but the spleen became the site of intensive erythropoietic activity. A severe and persistent anemia, which had been predicted, developed in splenectomized mice that had been injected with similar amounts of Sr(89-90).[17] Since strontium is almost exclusively a bone-seeker, the lymphatic tissues, including the spleen, were essentially unaffected by its beta radiation and therefore had the capacity to respond to the demand created by the destruction of bone marrow. Leading from this was the question of the nature and mechanism of the stimulus to the hematopoietic tissue of the spleen. The splenic erythropoietic transformation occurred in the absence of an anemia, and within three days! Another question that intrigued us was what would happen if, by some technique, we could destroy all blood-forming tissue in the body except that located in the spleen. This gave impetus to the spleen-shielding experiments described below.

* Mice used in these experiments were CF No. 1 females, 10-12 weeks old, raised by Carworth Farms — homozygous for recessive genes aa, bb, cc.

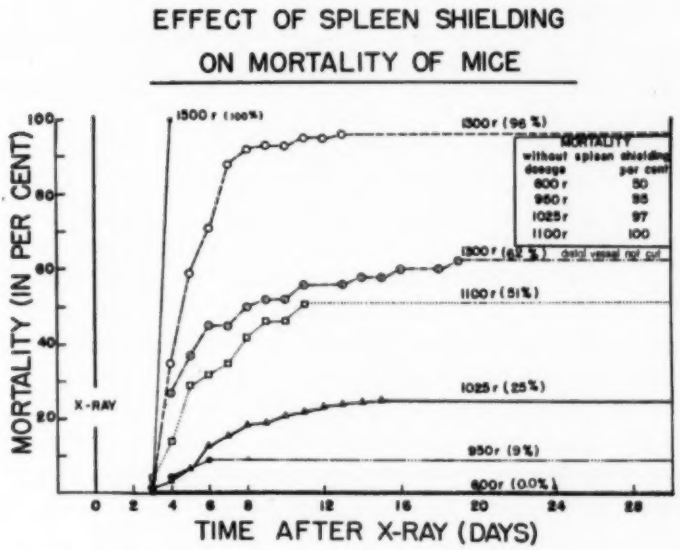

Figure 1—The effect of spleen-shielding on the mortality of mice following whole-body radiation.

The Effect of Lead-Shielding of the Spleen on Recovery from Radiation Injury

Lead-shielding of the surgically exteriorized spleen of adult mice during total-body x-irradiation markedly enhances survival (Fig. 1).[18] The survival of mice in which the circulation to the shielded spleen is clamped off during exposure and in which the clamp is released immediately after irradiation is approximately the same as the survival of animals with spleen-shielding without clamping.[16, 19, 20] The LD_{50} for total-body x-radiation is 600 r and the LD_{99} is around 700 r without spleen-shielding, whereas with spleen-shielding the LD_{50} is 1100 r and the LD_{99} is greater than 1300 r.[20] Histologic and hematologic studies have been made on animals that were exposed to 600 r, 900 r, 1025 r, or 1300 r. After 1025 r or 1300 r, recovery is more rapid and complete in spleen-shielded mice than in mice exposed to 600 r without spleen-shielding (Fig. 2). No anemia and only a transient leukopenia and thrombocytopenia follow an exposure to 1025 r with spleen-shielding,

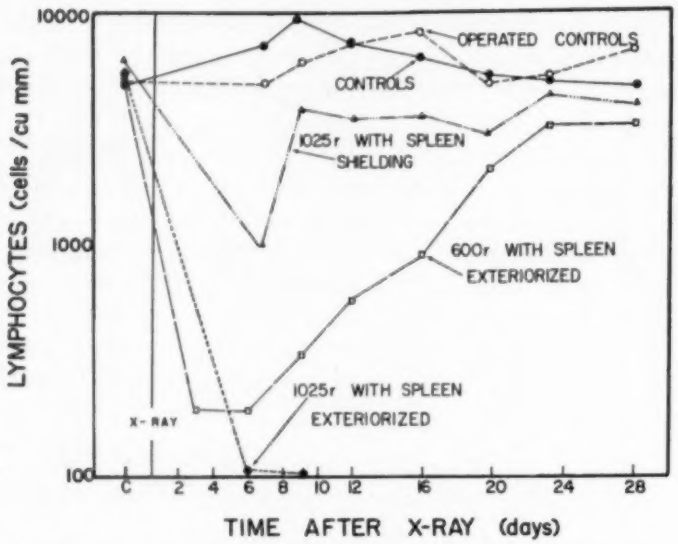

Figure 2—Comparative effect of 600 r whole-body irradiation without spleen-shielding, and 1025 r with spleen shielding on the lymphocytes of mice.

whereas pancytopenia and death follow this exposure without spleen-shielding.

The characteristic picture of destruction and atrophy that follows exposure to 1025 r was seen in both the spleen-shielded and non-spleen-shielded animals; recovery of bone marrow and lymphatic tissue began at four days and was complete by eight days in spleen-shielded mice, but no hematopoietic recovery was noted during this interval in non-spleen-shielded mice.[21] The prominence of heteroplastic activity in the bone marrow was considered to be particularly significant and is discussed in another part of this paper.

Shielding of other parts of the body of the mouse, such as a leg, a fraction of the liver, or the intestine, during x-irradiation in the lethal range (1025 r) increases survival, but less so than spleen-shielding, even though the volume shielded in each instance is much greater. For example, the survival of mice subjected to 1025 r with part of the exteriorized liver (0.8 gm.) shielded with lead is approximately 30 per cent compared with 76 per cent survival of mice with spleen-shielding.

The average spleen weight in these mice is 0.1 gm. Lead-shielding of 0.19 gm. of kidney does not enhance survival.

That post-irradiation therapy for radiation injury was feasible was evidenced by the fact that when the circulation of the shielded spleen was released to a mouse that had sustained a lethal exposure to x-radiation, it survived. Intensive blood formation, beginning at the 24-hour interval, was observed in the shielded spleens of the heavily irradiated animals. Serial sacrifice disclosed that erythropoiesis took precedence over other types of blood formation in the spleen. In fact, even the lymphatic nodules of that organ disappeared in some mice, and only the central artery of the nodule remained at the site of the original nodule. Essentially the entire spleen was transformed into an erythropoietic organ and remained so for several days before granulocytopoiesis and megakaryocytopoiesis became evident. Teleologically, one would have expected the reverse to occur, because, theoretically, the animal did not need erythrocytes since it was not anemic. Leukocytes to combat infection and platelets to insure capillary integrity and hemostasis were more likely requisites.

Whatever was saving the life of the irradiated animals appeared to have its source in the hematopoietic system because spleen-shielding was so much more effective in increasing the survival of mice and hastening the recovery of the blood-forming tissue than was the shielding of other body parts.

Whether survival was increased because the shielded spleen immediately took over blood formation and thus saved the animal from death due to pancytopenia and its complications was a pertinent question. Consequently, experiments were designed to determine how long the originally-shielded spleen had to remain in the circulation of the irradiated animal to insure survival. This was answered by the series of splenectomy investigations described in the following paragraphs.

The Effect of Post-Irradiation Splenectomy on Survival of Spleen-Shielded Mice

Splenectomies were performed at intervals, beginning at fifteen minutes after irradiation, on groups of mice that had been exposed to 1025 r x-radiation with spleen shielding (Fig. 3). As short a period as fifteen minutes was sufficient to increase survival. However, pancytopenia occurred in these animals, which was of greater severity and duration

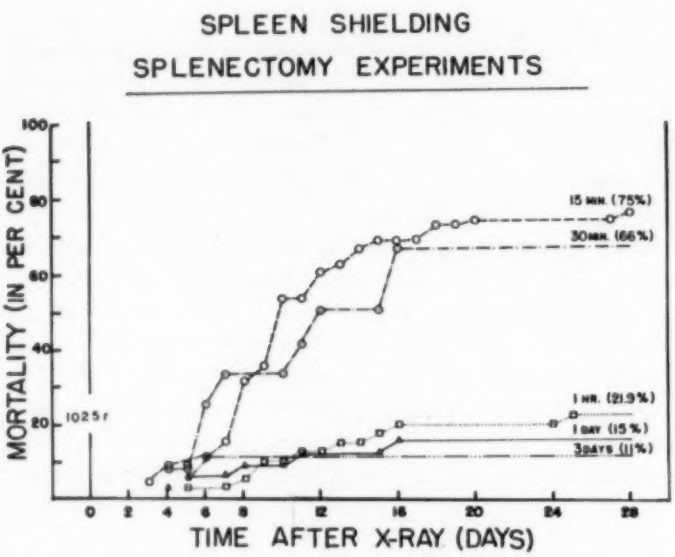

Figure 3—The effect of post-irradiation splenectomy on the mortality of spleen-shielded mice.

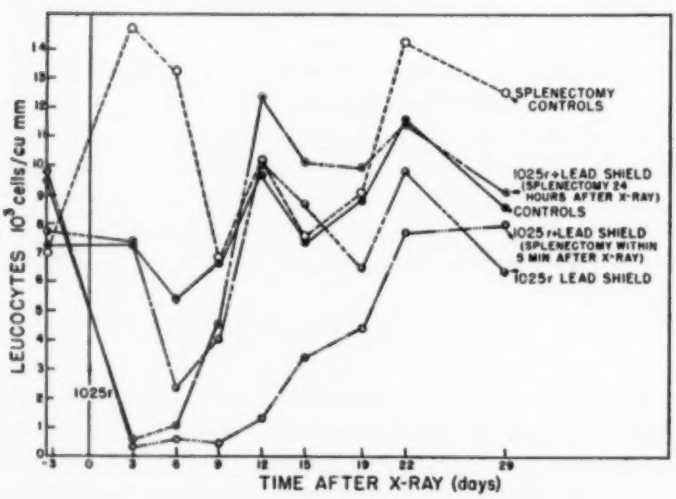
LEUCOCYTES 10³ cells/cu mm
SPLENECTOMY CONTROLS
1025r+LEAD SHIELD (SPLENECTOMY 24 HOURS AFTER X-RAY)
CONTROLS
1025r+LEAD SHIELD (SPLENECTOMY WITHIN 5 MIN AFTER X-RAY)
1025r LEAD SHIELD
1025r
-3 0 3 6 9 12 15 19 22 29
TIME AFTER X-RAY (days)

Figure 4—The effect of post-irradiation splenectomy on the leukocytes of mice.

than that observed in animals in which the spleen remained in the circulation for one hour. In those animals in which the spleen was left intact for one hour, survival (78 per cent) was comparable with that of the mice given routine spleen-shielding. It was noted that recovery of blood-forming tissue was more rapid and more complete in the animals in which the spleen was left intact in the circulation for the thirty-day period of observation (Fig. 4).

A small vessel at the distal end of the spleen was severed routinely to exteriorize the organ for the shielding procedure. This practice left the main pedicle intact, but up to one-half of the distal portion of the spleen was always infarcted. The survival of mice subjected to this exteriorization technique and 1300 r was 3.2 per cent, whereas survival was 31.2 per cent if the small vessel was left intact and no splenic infarction occurred.

Sometimes during the spleen-shielding procedure the entire splenic circulation was embarrassed by twisting of the spleen or stretching of the pedicle. When this happened, even before the spleen was returned to the abdomen, its deeply cyanotic appearance indicated that infarction of the entire organ would probably occur or had already occurred. Many of these animals lived. Sacrifice of some of these animals at appropriate time intervals proved to our satisfaction that infarction of the entire spleen had occurred and that splenic reconstitution began as the blood supply to the spleen was reestablished. The partially reconstituted spleen had the capacity to initiate the recovery process, and, thus, splenic transplants might very well be an effective means of bringing about the recovery of irradiated animals. If circulation to splenic transplants would become established in the irradiated hosts, then the procedure should increase survival and effect recovery of blood-forming tissue.

The Effect of Splenic Transplants and Other Homologous Tissue on Recovery from Radiation Injury

Spleen Transplants: Early attempts using spleens from adult mice for the transplants failed. This was assumed to be due to the fact that the adult spleens, placed randomly in the peritoneal cavity, did not usually develop a vascular supply. Later, we discovered that if the capsule of the transplanted adult spleen was cut before it was placed in the peritoneal cavity, it vascularized and significantly enhanced survival.

TABLE I—THE EFFECT OF SPLEEN IMPLANTS ON THE SURVIVAL OF IRRADIATED MICE.

Number of mice used	*Spleen implants within ½ hour after irradiation*	*Survival (per cent)*
112	None	0
63	4 spleens from 1-12-day-old mice	38
18	2 spleens from 4-5-week-old mice	45
24	4 spleens from 1-8-day-old mice implanted 2 days after irradiation of the recipient	20

From Jacobson, L. O. et al,[19] *Science 113*:510-11, 1951. Reprinted by permission.

The initial failure with mature spleens prompted a trial with the spleens from baby mice. Spleens (10 to 50 mg.) from normal baby mice ranging in age from one to twelve days were implanted intraperitoneally through a small slit in the abdominal wall of mice that had been exposed to 1025 r total-body x-radiation. No attempt was made to anchor the implant. Thirty-eight per cent of the irradiated hosts survived (Table I). Even if the animals received the spleens as late as two days after irradiation, appreciable survival was observed (25 per cent).

The quantity of tissue that the irradiated mouse received could be related to survival. For example, there was 38 per cent survival with 10 mg. of baby spleen but none with 5 mg. This was to be expected since survival had been found to be less in animals in which a partial splenic infarction had been produced deliberately than in animals in which no splenic infarction had occurred.

We considered these observations on survival and others on recovery of blood-forming tissue to be evidence of a quantitative relationship between the amount of tissue furnishing the necessary factor or factors to the irradiated animal and its survival or recovery from irradiation.

One of the experiments in which baby spleens were transplanted yielded some especially interesting results. Mice were exposed to 1025 r total-body x-radiation and were each given intraperitoneally four baby spleens. When the animals were autopsied, there was no trace of the original transplant in four of twelve mice that survived the twenty-eight-day period of observation. In one of the twelve mice only one splenic transplant was found; in three of the mice, two were found; in one, three of the transplanted spleens were found; and in three of the mice, four spleens were found.

TABLE II—THE EFFECT OF EMBRYO SUSPENSIONS ON THE SURVIVAL OF IRRADIATED MICE.

Group	*Number of mice*	*X-ray exposure (r)*	*Embryo Suspension*	*Per Cent Survival*
Control	123	1025	No	0.8
Treated	123	1025	Yes	30.0

It may be that the transplants vascularized temporarily and were later detached and removed by phagocytosis, or that cells from the splenic transplant migrated out before death and absorption of the transplant occurred. Whatever the fate of the transplant, it effectively altered the fate of the animal.

Embryo and Spleen Preparations: Study of the effectiveness of embryo and spleen preparations was stimulated by the observations that splenic transplants from baby mice increased survival and that mice occasionally survived 1025 r even though the transplanted tissue could not be found. Mouse embryos (fourteen- to twenty-day), taken by cesarean section, were ground in saline and administered intraperitoneally to mice exposed to 1025 r. Survival was found to be about 30 per cent (Table II).[16]

Spleens from one- to nine-day-old mice were mashed through a tissue press and suspended in buffered saline. Mice that had been exposed to 1025 r and which were injected intraperitoneally with this suspension did not survive. In point of fact, these mice died earlier than was expected from the radiation alone. If, however, the mice were exposed to 800 r, an intraperitoneal injection of this material significantly increased survival.[21] Lesser amounts of the suspension were later found to reduce the toxicity of the preparation and decrease mortality following exposure to 1025 r. The toxicity of splenic suspensions is reduced if the cells are extracted from the spleen immediately after it is removed from the body of the donor mouse. To do this, the cells may be washed from the spleen by multiple injections of saline or Locke's solution, by gently mashing the spleen in a mortar, or by pushing the splenic tissue through a 2-cc. syringe. The survival is approximately 75 per cent in animals exposed to 900 r and then given an intravenous injection of splenic cell suspensions prepared by any of these methods.

Our attention was directed to the so-called reticuloendothelial system as the richest source of the effective substance or substances[16] by the fact that survival of the irradiated animal is not altered by control transplants, suspensions, or the shielding of such tissues as muscle, kidney, or placenta, whereas it is increased by transplants or shielding of major blood-forming tissues such as liver, spleen, or leg. Bone marrow transplants and injections, which had been tried previously and reported of no value in dogs,[22, 23] were thus suggested as the next avenue for investigation.

Homologous Bone Marrow: The efficacy of bone marrow in increasing the survival of irradiated mice was first reported by Lorenz,[24] who found that 75 to 90 per cent of mice given a single exposure to 900 r survived if they were injected intravenously after irradiation with a suspension of homologous bone marrow. In addition to corroborating his findings, we[16] have found that the intravenous injection of bone marrow cells also significantly increases the survival of mice exposed to 1025 r. An assessment is in progress of the optimum and minimum number of cells from bone marrow, spleen, or embryo suspensions that will produce significant survival. Results from preliminary studies seem to indicate that cell suspensions of the soft portions of the embryo are more effective than suspensions of spleen or bone marrow. Each preparation that is used for these studies is adjusted in such a way that a comparable number of cells from each source is administered. The variability in results with different numbers of cells from bone marrow, spleen, or embryo suggests that the type of cells in the injected suspension may be a determining factor. For example, the endosteal, reticular, and endothelial cells may be of greater importance in initiating recovery than erythroblasts, myelocytes, and megakaryocytes. Preparations from the various sources are being studied to determine actual cellular make-up and the proportions of the constituent cells. It may then be possible to relate cell type to survival.

Heterologous Tissue: Survival studies on irradiated rabbits that had been treated with baby mouse spleen transplants indicated that regeneration of the hematopoietic system of the rabbit was stimulated by this procedure.[16] It has more recently been demonstrated by Lorenz and Congdon that the intravenous administration of guinea pig bone marrow[25] or rat bone marrow[26] markedly increases the survival of mice that have been exposed to lethal amounts of x-radiation. We have cor-

roborated their findings on the effectiveness of rat marrow in mice.[27]

That the fate of individual injected cells is not known with any degree of certainty has already been stated. Whether suspensions of heterologous and homologous bone marrow or (washed) spleen cells implant in the body and live a "normal life span," or whether these cells function only temporarily as normal cells is an open question. For example, we do not know whether the rat hematopoietic cells that are injected into an irradiated mouse function in phagocytosis and divide and multiply. These cells, by some mechanism, however, succeed in altering the pathologic state of the irradiated animal to the extent that the animal recovers.

Recovery of the blood-forming tissue may initiate or foster the recovery process in irradiated animals treated by one of the various techniques under discussion. We know that recovery of bone marrow and lymphatic tissue is initiated under these circumstances by four days after irradiation (perhaps earlier if methods of studying functional reconstitution of cells become more refined). Miller et al.[28] have shown that the normal function of these tissues is essential to combat infection. By way of speculation, however, one might logically raise the question of why the overwhelming infection, which is described, comes relatively late after lethal irradiation, while destruction of the blood-forming tissue is manifest soon afterward. Is the animal protected against bacterial invasion during the first week after irradiation by some mechanism or agent that is quite apart from the hematopoietic tissue?

One must not conclude from this that because blood-forming tissue does recover it is the only one vital to survival. Such tissue as liver may also be important. The development of more sensitive methods to study the in vivo inhibition and recovery process of these tissues after irradiation may be quite revealing. In fact there is now good evidence that recovery of blood-forming tissue is not the sole factor essential to recovery. The data referred to above support this; namely, that only circa 30 per cent of animals survive 1300 r with spleen-shielding and preservation of the entire splenic circulation, whereas 3.2 per cent survive if the spleen is shielded and only part of the splenic pedicle is preserved. In the splenic circulation group there should be almost 100 per cent survival if recovery of blood-forming tissue were the only factor involved. Williams et al.[29] have reported experiments in which the entire body of the rat was shielded except for an exteriorized segment of the

small bowel. The rate of recovery of the bowel epithelium in this segment was not appreciably different from that observed in control nonshielded animals. Their work implies that recovery of bowel epithelium or failure to recover from radiation injury is largely, if not entirely, unrelated to the state of the blood-forming tissue. These observations emphasize the limitation of the "therapeutic" techniques described in this communication and direct our attention to other systems that are vital to recovery from radiation injury. The radiosensitivity of cells in various tissues in the body such as the brain, thyroid, and gonads varies widely. Cells derived from a single source, such as the reticulum of the blood-forming tissue, have different radiosensitivities.[30] There is evidence to show that various functions of the same cell have different radiosensitivities. For example, reticular cells are capable of phagocytosis. This function is extremely radioresistant, and exposures above 100 r do not seem to affect it (histological observation), whereas heteroplastic or homoplastic multiplication is inhibited by about 500 r. It may also be assumed that with increasing exposures not only are more and more functions of the reticulum eliminated, but other cells in the body are similarly affected.

Allied Studies

Synergistic Action of "Prophylactic" and Therapeutic Measures on Radiation Injury: That compounds such as estradiol and cysteine enhance the survival of irradiated animals when given prior to irradiation is mentioned in the introduction. Such prophylactic measures combined with post-irradiation measures such as spleen-shielding have an additive effect on survival.[31, 32] The findings, however, do not necessarily imply that the mechanism of action of both procedures is identical.

Attempts to Extract the Factor or Factors from Hematopoietic Tissue: We have made a number of attempts to obtain a cell-free extract of spleen, embryo, or bone marrow that would increase the survival of irradiated mice. Thus far, our results have been only negative or equivocal. Simple buffered saline extracts of spleen, bone marrow, or embryo or homogenized preparations of such tissue produce negative results if the material is filtered so that no cells or parts of cells are present.

Cole and his co-workers[33, 34] claim to have prepared suspensions of mouse spleen cells with only the nuclei of the cells intact. According to their report, such preparations, when administered intraperitoneally

to x-irradiated mice routinely increase survival. If, indeed, these suspensions contain no intact cells and thus no living cells in the ordinary sense, then additional proof for the humoral theory is at hand. The need for a simple and sensitive method to assay the activity is obvious since identification of the effective substance or substances in the whole cell or the nucleus is still unsolved. Survival following lethal irradiation is being used as the yardstick for measuring the effectiveness of various cell suspensions or preparations free from living cells. This method appears to be much too insensitive.

Relations of Species and Strain to the Effectiveness of Spleen-Shielding or Injection of Hematopoietic Cell Suspensions: The phenomenon of hastened hematopoietic recovery as well as increased survival in animals x-irradiated in the midlethal or lethal range with spleen-shielding is not confined to the mouse. Lead-shielding of the spleen of rats, guinea pigs, and rabbits during midlethal exposures is followed by a more rapid recovery of the hematopoietic tissue and a reduced mortality. However, there is a pronounced difference in the species response to the techniques under discussion. Spleen-shielding in the mouse, for example, spectacularly increases survival and markedly hastens the recovery of blood-forming tissue, whereas a definite but minimal effect is observed in the rabbit. This may be due to a quantitative difference in the capacity of the rabbit spleen or appendix to produce the substance or substances necessary for the recovery process.

There are also strain differences. Studies of six different strains of mice have revealed that spleen-shielding or injection of suspensions of hematopoietic cells after total-body x-irradiation effectively increases survival of all of the strains and hastens hematopoietic regeneration, and that bone marrow, spleen, or embryo suspensions from one mouse strain are effective in another strain. However, in one particular strain (CF No. 1) the LD_{50} with spleen-shielding is about 1100 r whereas in another mouse strain (Webster) the LD_{50} under similar circumstances is 1000 r.

Effect of Spleen-Shielding on Antibody Formation: It is well known that total-body x-radiation inhibits antibody formation in laboratory animals.[35,36] The capacity of rabbits exposed to 800 r total-body x-radiation with spleen- or appendix-shielding to produce antibodies in response to an intravenously administered particulate antigen is retained, whereas without shielding this capacity is suppressed.[37] In fact, the antibody

response to an injected antigen is retained in irradiated rabbits even though the originally-shielded spleen is removed twenty-four hours after the shielding-irradiation procedure and the antigen is given forty-eight hours after the exposure (24 hours after splenectomy).[38] In the experiments referred to above, the antigen was administered (both in the experimental and control animals) when the cellular hematologic constituents of the peripheral blood were greatly reduced, cell death and phagocytosis of hematopoietic tissue was continuing, and there was no evidence of regeneration. Nevertheless, antibody formation was initiated in the spleen-shielded splenectomized animals but not in the non-spleen-shielded animals. Data are also available indicating that the shielded spleen need only remain intact in the circulation of the rabbit for three hours after total-body x-irradiation to restore significantly the capacity to produce antibodies.[39]

Disscussion of Theories on Mechanism of the Effect of Spleen-Shielding and Related Techniques on Recovery from Radiation Injury

The theories on mechanism of the success of these techniques that have been obvious to us since the original observations are three:

1. Detoxification of substances produced by irradiation.
2. Cellular seeding and tissue reconstitution.
3. Production of a humoral substance that initiates functional reconstitution of cells.

It has long been assumed that irradiation produces a toxin that has an inhibitory effect on metabolic processes within the irradiated cells. Transport of this "toxin" from the irradiated site to other parts of the body also is presumed to inhibit cellular processes at distant nonirradiated sites. The hydrogen peroxide, produced along the path of ionization, has been suggested as the toxic agent.[40] It is conceivable that the local and distant effect may be the result of the action of this or some other oxidizing substance. However, if this is true, one must assume that the production and dissemination of the substance and the initiation of the biologic effects occur within a relatively short time after irradiation and that the "toxin" is then destroyed or neutralized. Evidence for this is briefly as follows. After the administration of lethal amounts of radiation to groups of mice with or without spleen-shielding, the initial pathologic effects are identical, i.e., destruction and atrophy of the lym-

phatic tissue and bone marrow proceeds in both experimental groups at the same rate and reaches the same maximum. The observable difference in the two groups is that recovery of the blood-forming tissue begins by the fourth day in the spleen-shielded group and about 75 per cent of animals survive, whereas there is little or no histologic evidence of recovery of the blood-forming tissue in the non-spleen-shielded group and death is inevitable. If one removes the spleens from these two experimental groups one hour after irradiation, survival and recovery of hematopoietic tissue is nil in the non-spleen-shielded group, whereas survival is 75 per cent and recovery of hematopoietic tissue begins at four days in the spleen-shielded animals. If a toxin is indeed responsible for the destruction and continued inhibition of cells, it must be a transitory one or it would continue to act beyond the one hour during which the spleen is left intact in the circulation in the spleen-shielded group, and these animals would not be expected to recover. It seems unlikely but it cannot be denied, however, that while the spleen is in the circulation it may continue to neutralize the toxin and that after the organ is removed its cells that were disseminated throughout the body carried on the detoxification process. This aspect will be discussed more fully.

Another interesting observation that might be used as evidence against the continuing production and dissemination of a toxin is that the injection of spleen cells or bone marrow reverses the otherwise lethal effect of radiation even when either is administered two or three days after an animal had been exposed to a lethal amount of radiation.[41] If a specific toxin were entirely responsible for the destruction and continued atrophy and inhibition of cells and organ systems, one might logically expect an increasing pathologic state. It has been suggested by Storer and Lushbaugh[42] that the effectiveness of shielding is related to the capacity of the shielded tissues to forestall infection until the tissues of the body and especially the blood-forming tissue can regenerate spontaneously. This seems an untenable explanation for a number of reasons, one of which is the fact that the shielded spleen of the mouse can be removed an hour or less after the administration of a uniformly lethal total-body exposure and yet the animal survives. The effectiveness of heterologous cells (rat to mouse, guinea pig to mouse, and mouse to rabbit) in bringing about recovery makes Storer's postulate even more untenable, unless such heterologous cells function in the new host in a manner largely comparable to normal homologous cells in terms of com-

bating infection and the like.

The theory that shielded tissue and injected hematopoietic cell suspensions may cause a reversal of the lethal effects of radiation by seeding destroyed hematopoietic tissue throughout the body is attractive but seems unlikely. The effectiveness of heterologous tissue makes this theory rather remote. One cannot ignore the data from histologic observations that indicate that hematopoietic regeneration in the bone marrow from reticular cells and osteoblasts is prominent in spleen-shielded mice or mice injected with cell suspensions. If seeding via the blood stream and subsequent regeneration by multiplication of cells is a factor in the regeneration, then the release of the inhibition of the reticular cells, allowing them to multiply, would still have to be explained.

It would appear more reasonable that the effect produced by lethal irradiation represents a chain of events initiated by an agent such as hydrogen peroxide, and that the profound effect of spleen-shielding, or injection of such materials as embryonic tissue, spleen or bone marrow cells and the like could best be explained by assuming that these cells or tissues provide one or more of the metabolites necessary for the functional reconstitution of the injured cells. Cole's observations[33,34] and the effectiveness of heterologous tissue materially strengthen this hypothesis.

Summary

Whole-body exposure to ionizing radiations in the lethal or midlethal range produces widespread destruction of certain tissues in the body such as blood-forming tissue, the gastrointestinal tract, and the gonads. Death may be related to injury of one or more tissues and organ systems, but the destruction and delayed recovery of blood-forming tissue is considered to be one of the more critical. A number of prophylactic measures such as the injection of cysteine and glutathione just prior to irradiation will reduce mortality. These materials have no beneficial effect if given afterward. Measures that in effect are instituted after lethal irradiation, e.g., spleen-shielding or the injection of spleen cells, suspensions of spleen or embryo cells, and bone marrow, increase survival and hasten recovery of blood-forming tissue. The mechanism of this striking effect is unknown. The possibilities considered are: 1) detoxification of some radiation-produced toxin; 2) seeding of the animal with injected cells that multiply and repopulate tissue such as the bone marrow; and 3) production of a humoral substance or substances by the

shielded or injected cells that brings about functional reconstitution of the inhibited cells and initiates regrowth of vital tissues. On the basis of a number of observations, including the pattern of histologic recovery in spleen-shielded animals, and the fact that heterologous tissue (i.e., rat to mouse) effectively enhances the survival of irradiated mice, the humoral theory seems the most acceptable.

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DIFFERENTIATION OF SERA ON PHENOL*

(A preliminary report)

EUGENE S. SAGI and JULES PLESS

Clinical Discussion

LOCKE L. MACKENZIE**

WHILE investigating a group of physico-chemical properties of protein solutions, a study was made with systems of opposite actions. One such system was concerned with the behavior of phenol toward proteins. Phenol, when dissolved in water, precipitates certain proteins out of their aqueous solutions, while the concentrated phenol dissolves the same proteins. These phenomena, insofar as the time element is involved, can best be observed when a drop of the protein solution is placed on the surface of concentrated phenol. First a precipitation takes place, which is then followed by the dissolution of the precipitate in the bulk of the reagent.

After it had been established that different proteins, at the same level of concentration, yielded different patterns of precipitation and dissolution, and that the serum of two species of animals showed rather characteristic changes in the appearance of the drop on phenol, it was decided to investigate human serum. It had been expected that some differences in the formation of the drop might occur, depending upon physiological and pathological conditions.

In the first series, results were sufficiently encouraging to warrant an investigation on a broader basis, and to improve the method.

The striking difference in the precipitation and subsequent dissolution of a drop of human serum, placed on the surface of phenol, established two types of patterns: 1) the stable drop (negative reaction), and 2)

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the disintegrating drop (positive reaction). The negative reaction appears in the sera of healthy individuals and in patients with most nonmalignant diseases. The positive reaction is seen in sera in cases of malignant pathology, and in a distinct group of nonmalignant diseases which will be discussed later.

Method

Reagent: 75 ml. of liquefied phenol (88 per cent) is mixed with 25 ml. of glycerin. To this mixture a 10 per cent NaOH solution is added to obtain a pH of 8.0.

Equipment: Pipette: a one ml. pipette with an 18 gauge needle. The point of the needle is filed off smoothly and this needle is hermetically sealed to the pipette.

Slide with cavities: the conventional agglutination slide, having 12 cavities.

Temperature: 20°C to 23°C seems to be the optimum temperature of the system. A constant temperature workroom is indispensable.

Preparation of serum: 4 to 6 ml. of fasting blood is required. Glassware must be free of impurities, especially of acid, alkali, or detergents. The blood must not be put in the refrigerator before the serum has been separated. After separation by centrifuging, the serum is incubated at 33°C for four hours in a waterbath. After such incubation, the serum is cooled off in a refrigerator for half an hour, although it may be left in the refrigerator for two to three days before testing at room temperature.

Technique: The agglutination slide is cleaned with running tap water, dried, and the cavities wiped with fine tissue paper, preferably lens paper. Into each cavity is placed 0.12 ml. of the reagent, and the slide is placed over a dark background. The pipette is rinsed once with physiologic saline solution. The rinsing fluid is allowed to run freely out of the pipette until the meniscus reaches the tip. The remaining fluid is blown out, the tip of the needle is wiped with gauze. The serum is drawn gently into the pipette and released back into the test tube, blowing out only the remainder in the tip. A second column of serum is now drawn, and the stem and the tip of the needle are wiped off. This procedure precludes the adherence of air bubbles to the wall of the pipette. The tip of the needle should be frequently checked by a magnifying glass and any irregularities corrected with 0/1 sandpaper. The per-

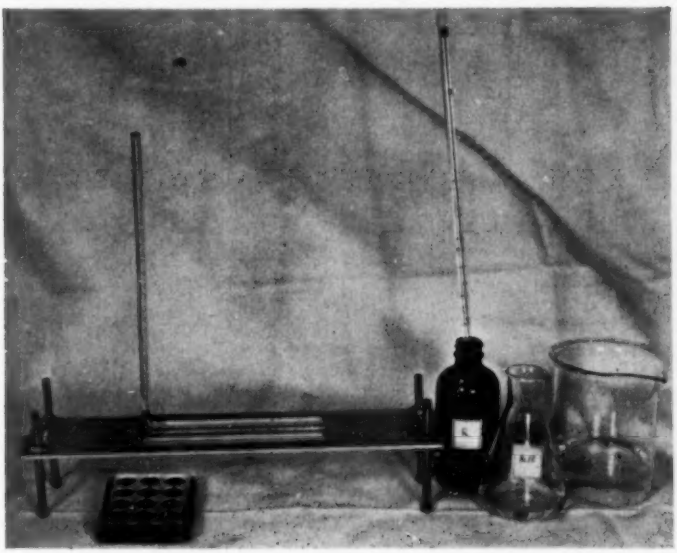
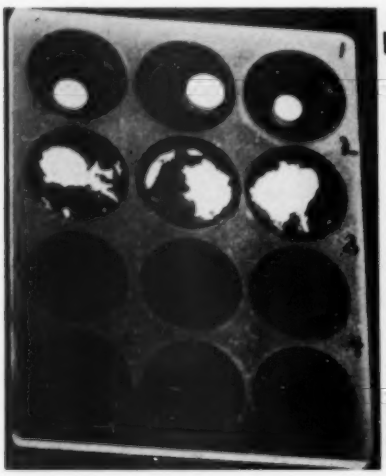


Figure 1—Stand, Pipette, Slide.

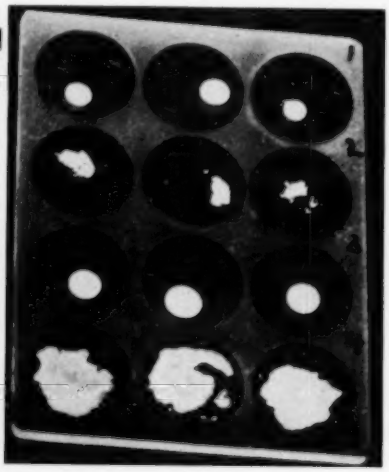
formance of the test is greatly facilitated by the use of a metal frame which supports the pipette and regulates the distance through which the drop falls to the surface of the reagent. One drop of serum is allowed to fall from a distance of 6 mm. upon the center of the surface of the reagent. The fallen drop, when properly released, submerges into the reagent without bursting or being distorted. Distortions are likely to occur whenever the pipette is not firmly supported or held in a perpendicular position aimed at the center of the cavity, or when air bubbles are adhering to the tip of the pipette, or when air has been drawn into the pipette together with the serum. It is necessary to avoid faulty release and to achieve uniformity in the dispensing of the drop. Routinely, one drop of serum is deposited into each of three adjacent cavities for each specimen.

Reading: In the negative reaction, the fallen drop entering the reagent submerges and within a moment arises to the surface in the form of a discrete pellet. It then contracts into a smaller pellet and remains floating on the surface for approximately one hour. During this period



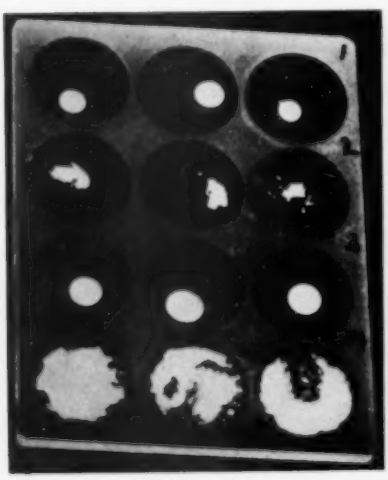
A

Row 1—negative reaction
Row 2—delayed positive reaction in 5 minutes
(Rows 3 and 4—not used)



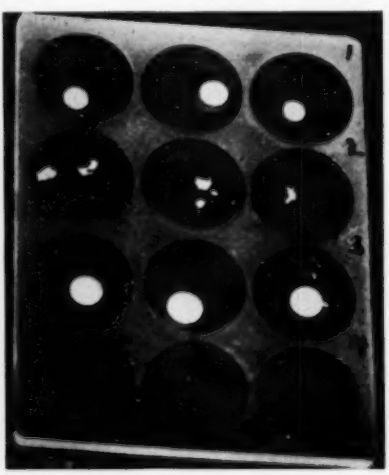
B

Rows 1 and 2 same as A, 5 minutes later
Row 3—negative reaction
Row 4—positive reaction in 10 seconds



C

Same as B—1 minute later



D

Same as C—2 minutes later

Figure 2—The phases of the negative and the positive reaction

the pellet gradually grows smaller until it disappears in the surrounding liquid.

In the positive reaction, the fallen drop, upon rising to the surface does not contract but, instead, it spreads into a thin film and unfolds over the greater part of the surface. Within eight to twelve seconds the fragile film falls apart into minute particles which rapidly dissolve in the surrounding liquid. Infrequently, the fallen drop neither contracts nor unfolds, but expands into a moderately resistant film with serrated circumference which remains floating for as long as twenty minutes before dissolving in the reagent. Such appearance does not constitute a separate pattern but is to be read as a positive reaction.

It is recommended that each row of three cavities be marked with the series number of the specimen. After the test has been performed, the slide is set aside for the final reading.

The method and technique of the procedure have been developed entirely by empiric observations. The changes in the composition of the reagent, the temperature, and the length of the incubation, and variation of the distance of the fall of the drop, all have a decisive effect on the forming of the pattern. Further experience might lead to useful modifications of the technique. However, it is now believed that the accumulation of large series of comparable data should be obtained using the technique here discussed.

Results

At the beginning of the study of clinical material, cases were encountered in which positive results occurred unexpectedly. In the majority of such cases, the reason for this apparent incongruity was found to be due to therapeutic procedures. These findings were later corroborated in the investigation of a larger series. The drugs and other therapeutic measures which seemed to have an influence on the outcome of the reaction will be enumerated.

In the course of the study, it was shown that advanced pregnancy, uncontrolled diabetes, and a few other diseases, which can be readily diagnosed, may also give positive reactions. These diseases will be listed.

The following clinical groups have been established:

Group I. Blood donors and employees of food establishments. The latter group underwent semi-annual examinations particularly designed to rule out tuberculosis and syphilis. In this group of 1,500 "well"

TABLE I—ILLUSTRATES THE DETAILS IN GROUP II

Administration within 72 hours before test	*Number of cases*
Penicillin	21
Aureomycin	11
Streptomycin	10
Terramycin	6
Chloromycetin	5
Dicumarol	12
Salicylates	10
Steroid hormones	16
Transfusion of whole blood or plasma, infusion of saline or glucose or protein hydrolysates	9

people, there were 1,498 negative and two positive tests.

Group II. Patients treated with antibiotics, anticoagulants, salicylates, and steroid hormones, or those who received transfusion or infusion. There were 100 patients in this group; ninety-two were positive and eight were negative (Table I).

In eleven cases the opportunity was afforded to follow simultaneously both the test and the cycle of administration. Tests were negative before administration, became positive during the administration, and reverted to negative in three to ten days after the discontinuation of the administration. In all of these cases the positive reaction appeared approximately twenty-four hours after administration, and in only five did the positive reaction persist for more than seventy-two hours. In three cases with penicillin, in two with salicylates, and in three with transfusion the reaction remained negative.

Group III. Advanced pregnancy (beyond the fifth lunar month), uncontrolled diabetes, uncontrolled pernicious anemia, glomerulonephritis, nephrosis, extrarenal azotemia, viral hepatitis, and advanced cirrhosis of the liver, described above as a distinct group. In this group of eighty cases, seventy-eight gave a positive and two a negative reaction. Here there were thirty-four in advanced pregnancy, eighteen with uncontrolled diabetes, six with cirrhosis of the liver with ascites, five with glomerular nephritis, five with extrarenal azotemia, four with pernicious anemia, three with nephrosis, three with virus hepatitis, and two with

TABLE II—HEMOGLOBIN VALUES IN 493 CASES WITH NONMALIGNANT PATHOLOGY

Grams hgb. per 100 ml.	*No. of cases with negative reaction*	*No. of cases with positive reaction*
7-8	28	1
8-9	41	2
9-10	97	5
10-11	144	4
11-12	83	2
12-13	35	3
13-14	37	2
over 14	9	0

Banti's disease. In one of the cases with Banti's disease a splenectomy was performed; three weeks later the reaction became negative. Eleven cases of diabetes were available for study of the correlation between varying blood sugar levels and the reaction. The test was found to become negative at about 120 mg. of glucose per 100 ml. while above this level, with one exception, the positive reaction appeared.

Group IV. Patients with nonmalignant pathology, excluding the two preceding groups. There were 970 such cases. Tests performed on these resulted in 933 negative and thirty-seven positive reactions.

This group consisted of patients chosen at random from the population of general hospitals. They included a large number of acute and chronic inflammatory diseases, wasting and chronic debilitating diseases, benign tumors, and localized anatomical lesions of various organs. Among them, approximately 680 were in a more or less advanced stage of disease. They were clinically in poor general condition. In this group both hemoglobin and total serum protein values of the same patients were available in 474 cases with negative and in nineteen cases with positive reaction (Tables II and III). These tables serve the purpose of (a) illustrating that the negative or positive outcome of the reaction is independent of the total serum protein concentration, and of (b) indicating the nutritional and general clinical state of the patients, insofar as such values express these conditions at all.

TABLE III—TOTAL SERUM PROTEIN VALUES OF THE SAME 493 CASES AS IN TABLE II

Grams total serum protein per 100 ml.	*No. of cases with negative reaction*	*No. of cases with positive reaction*
5.3 - 5.8	39	3
5.8 - 6.3	116	5
6.3 - 6.8	126	4
6.8 - 7.3	104	4
7.3 - 8.0	81	2
over 8.0	8	1

Group V. This group included patients with surgically removed malignant tumors, and those who, after operation, have received irradiation, as well as those who were irradiated without the removal of the lesion (inoperable cases, leukemia); also those receiving steroid hormones with or without removal of the neoplasm. Forty-one cases were available in this group; thirty-eight had negative and three had positive reactions (Table IV, see page 703).

Group VI. Frank malignancy. There were 357 cases available; thirty gave the negative and 327 the positive reaction. This group consisted of patients before, or shortly after operation. They did not receive irradiation and were not treated with hormones. In it are included local recurrences, metastases developing after the primary lesion had been removed, Hodgkin's disease, and leukemia (Table V, see pages 704-5).

It has also been attempted to indicate the nutritional and general clinical state by values of hemoglobin and total serum protein (Tables VI and VII, see page 706).

Some significance may be attributed to the positive reaction in the following cases as an indication of the use of the test in the early detection of malignancy and as a differential diagnostic aid.*

1. (B) 38961-52. Male, 72. **Hematuria started 2 weeks ago, no clots, occasional burning on urination. The resectoscope revealed a papillary growth on the floor of the bladder. Tissue pathology reported: papillary adenocarcinoma.**

2. (M) 6572. Female, 28. **Routine examination revealed a cystic mass in the region** of the right ovary, no presenting symptoms. At operation a cyst of the salpinx, 7-8

* (B): Bellevue Hospital, New York. (J): Jewish Hospital of Brooklyn, New York. (M): Methodist Hospital of Brooklyn, New York. (U): University Hospital, New York.

cm. in diameter, was found. No other involvement. Tissue pathology: endosalpingioma (papillary intracystic serous cystadenocarcinoma).

3. Female, 44. No complaints. Both parents died of cancer. Patient wanted a checkup. Negative clinical findings; vaginal cytology negative. Three months later protracted menses, cancer cells in smear. Operation and tissue pathology revealed cancer in situ of the cervix.

4. (B) 27817-52. Male, 66. Three weeks ago patient's attention called by dentist to a lesion in the central floor of the mouth; 2-3 mm. elevated firm growth, no marked fixation. No cervical or submaxillary lymphadenopathy detected. Initial biopsy: leukoplakia. Second biopsy: Squamous cell carcinoma. Tumor removed, no nodes.

5. (B) 26203-52. Female, 39. Six weeks ago, twice, moderate rectal bleeding. Since then no bleeding. No diarrhea, no constipation, no weight loss. Only complaint: pain when working, localized in sacrum. Biopsy: soft cauliflower lesion of rectum, adenocarcinoma. Operation: small polypoid tumor of rectum, no metastases.

6. (M) 5225. Female, 37. Presented herself with chief complaint of dysmenorrhea. Pelvic examination revealed a lesion of the cervix which resembled central cervicitis. Cytology: questionable. Operation and tissue pathology: carcinoma in situ, minute focus.

7. (J) 329080. Male, 71. Admitted with pains localized to R.L.Q. Diagnosis: acute appendicitis. Operation confirmed appendicitis; the hepatic flexure was palpated, and a firm granular mass was felt. Two weeks later colectomy performed: tumor 3.8 cm in length. Tissue pathology: adenocarcinoma, adenomatous polyps in colon, in one polyp carcinomatous change.

8. (M) 6046. Male, 12. C.C. fatigue, weight loss, pallor, and intermittent fever. Clinical findings negative, except bone marrow not inconsistent with Hodgkin's disease. Exploratory laparotomy revealed multiple abdominal nodes which were reported as Hodgkin's granulosarcoma.

9. (B) 1887-51. Male, 50. Postive findings were limited to two marble sized masses in the neck. Also noticed retinitis pigmentosa. Later lymph node biopsy: either lymphepithelioma or reticulum cell sarcoma.

10. (B) 38308-52. Female, 72. Admission for rehabilitation following a fracture of femur. During hospitalization a kidney shaped mass was detected in the R.L.Q. At operation a hard mass was found involving cecum and ascending colon with metastases to nodes. Tissue pathology: carcinoma of cecum with extension to pericecal adipose tissue.

11. (J) 305596. Female, 63. Two years ago hysterectomy and bilateral salpingo-oophorectomy performed because of fibromyomata, confirmed by tissue pathology. Preoperative diagnosis: empyema of gall bladder. At operation: empyema of gall bladder with multiple stones, and a tumor of the gall bladder were found; in the liver many metastatic nodules. Carcinoma confirmed by tissue pathology.

12. (U) K 48797. Female, 61. Severe abdominal pain, weight loss in 3 weeks of 12 lbs. Negative clinical findings, no conclusive diagnosis established. Exploratory laparotomy: secondary malignant teratoma in omentum, primary site undetermined.

13. (J) 32488. Female, 67. Six months prior to admission hospitalized for pulmonary emboli. Preoperative diagnosis: subphrenic abscess, though liver metastases a

possibility. At operation: empyema of gall bladder, multiple stones, and a tumor of the gall bladder were found; in the liver many metastatic nodules. Carcinoma corroborated by tissue pathology.

14. (U) K 53915. Female, 53. One month ago routine checkup showed mass in abdomen: no complaints. Diagnosis: pancreatic cyst. Exploratory laparotomy: 15 cm. tumor mass in the mesentery of jejunum. Tissue pathology: malignant lymphoma, type undetermined.

15. (J) 328473. Female, 53. Periumbilical pain, anorexia, lost 15 lbs. in three months. Physical examination revealed sense of slight fullness in the R.L.Q., otherwise negative. Preoperative diagnosis: appendicular abscess, though abdominal malignancy not ruled out. At operation appendicular abscess and carcinoma of the cecum with metastases to the liver were found.

16. (J) 326565. Male, 70. Admitted with jaundice, pruritus for 3 weeks, accompanied by darkening of urine and "white stools." G.I. series negative. Preoperative diagnosis: obstructive jaundice probably due to carcinoma of the head of the pancreas. Operation: hard tumor mass occluding common duct just above duodenum. Tissue pathology: glandular carcinoma of the common duct.

Among the thirty negative results in this group, the following are illustrated as examples of false negative tests.

Female, 58. Sixteen years ago radical mastectomy with removal of axillary lymph nodes performed. P.I. 3 weeks ago observed a swollen node in the neck. Biopsy: metastatic lymphadenopathy.

Male, 73. Adenocarcinoma of the stomach proven by operation and tissue pathology. No metastases.

Discussion

The precipitating action of aqueous phenol solutions is used in the examination of the spinal fluid (Pandy's reagent). The dissolving action of concentrated phenol has been the subject of several investigations to establish the mechanism of this action. Herzog and Krahn[1] as well as Troensegaard and Smith[2] advanced the theory that phenol induces disaggregation of the proteins into units of lower molecular weight, while in aqueous solution the proteins aggregate to larger units. Cohn and Conant[3] in their study on the depression of the freezing point of phenol by proteins, did not corroborate either the findings or the theory of the former authors. As yet, there seems no satisfactory explanation as to the mode of the protein dissolving action of the phenol or of the other organic protein solvents, such as anilin, cresol, and glacial acetic acid.

In order to establish the lowest concentration at which protein solutions show the pattern corresponding to the negative reaction, isolated human serum albumin, serum globulin, egg albumin, leukosyn of the wheat germ, and other vegetable proteins, were investigated. Serum

(*Discussion continued on page 706*)

TABLE IV—DISTRIBUTION OF THE CASES WITH REMOVED AND/OR OTHERWISE TREATED TUMORS

No. of Cases	*Site*	*Type**	*Regional Spread***	*Therapy*	*Interval†*	*Present Status††*	*Test* —	+
9	breast	5 adenoca. 2 scirrhus 2 ?	5 yes 1 no 3 ?	surgery	6 mos. to 18 yrs.	no evid.	8	1
5	stomach	4 adenoca. 1 ?	3 no 2 ?	surgery	4 mos. to 7 yrs.	no evid.	5	0
5	uterus	3 sq. cell ca. of cervix 2 adenoca. of body	2 yes 3 no	surgery	4 mos. to 5 yrs.	no evid.	4	1
3	chr. lymph. leukemia			2 irrad. 1 cortisone	1 to 6 mos.	decrease of wh. cells to 10%-30% of original count	2	1
2	lung	1 oat cell ca 1 broncho-gen. ca.	1 yes 1 ?	1 surgery 1 irrad.	6 mos. to 1 yr.	no evid.	2	0
2	colon	1 medullary ca. 1 colloid ca.	2 yes	2 surgery	2 yrs. to 4 yrs.	no evid.	2	0
2	rectum	1 papillary ca. 1 scirrhus	1 yes 1 no	2 surgery & irrad.	1 yr.	no evid.	2	0
2	prostate	2 adenoca.	2 yes	2 surgery & stilbesterol	1 to 3 yrs.	1 no evid. 1 metast. to bones	2	0
2	skin	2 basal cell ca.	2 no	2 surgery & irrad.	1 to 7 yrs.	1 no evid. 1 recurr.	2	0
2	urinary bladder	2 papillary ca.	2 no	1 fulgur. 1 surgery	1 to 6 yrs.	no evid.	2	0
2	tongue	2 sq. cell ca.	2 yes	2 surgery & irrad.	2 to 3 yrs.	no evid.	2	0
1	mandible	osteosarc.	no	surgery & irrad.	8 mos.	no evid.	1	0
1	buccal mucosa	adenoca.	yes	surgery & irrad.	6 mos.	no evid.	1	0
1	tonsil	adenoca.	yes	surgery & irrad.	6 mos.	no evid.	1	0
1	larynx	adenoca.	yes	surgery & irrad.	3 mos.	no evid.	1	0
1	penis	basal cell ca.	no	surgery	7 mos.	no evid.	1	0
							38	3

*? = no information available.
**yes = lymph nodes involved, no = lymph nodes not involved, ? = no information available.
†the period between surgical removal or start of last cycle of treatment and the test.
††no evid. = no clinical evidence of malignancy.

TABLE V—SITE, TYPE AND SPREAD OF 357 CASES OF MALIGNANCY

No. of Cases	*Site*	*Type*	*Regional Spread*	*Distant Spread*	*Test* —	+
53	stomach	39 adenoca. 11 gel ca. 3 diffuse ca.	37	3 liver 2 transv. colon	4	49
44	breast	20 medul. ca. 14 adenoca. 4 Paget's disease of the nipple 4 circumscribed scirrhus 2 small infiltr. scirrhus	21	11 axillary nodes 5 nodes in neck	2	42
38	uterus	23 sq. cell ca. of cervix 9 diffuse adenoca. 5 pap. adenoca. 1 fibrosarc.	19	6 bladder 3 intestines	2	36
25	lung	19 bronchogen. ca. 6 oat cell ca.	16	3 pleura	3	22
23	colon	18 adenoca. 5 colloid ca.	17	2 liver	2	21
19	prostate	19 adenoca.	6	6 bones 3 liver 2 bladder	3	16
16	urinary bladder	11 pap. ca. 5 diffuse adenoca.	11	1 rectum	2	14
12	pancreas	9 adenoca. of the head 3 adenoca. of the body	8	3 liver	1	11
11	rectum	adenoca.	5	3 large coalescent masses	1	10
10	ovary and salpinx	6 adenoca. 2 cystadenoca. 2 malignant teratoma	4	1 liver	0	10
7	sigmoid	4 adenoca. 3 pap. ca.	4	1 coalescent abd. mass	1	6
5	small intestines	3 pap. ca. 2 adenoca.	3		0	5
5	skin	3 basal cell ca. 2 sq. cell ca.	1		1	4
4	esophagus	4 adenoca.	4	2 mediastinum	0	4
4	tongue	4 sq. cell ca.	2		0	4
4	mucosa of the mouth	4 adenoca.	2		2	2
3	pharynx	3 adenoca.	1		0	3
3	liver and bile ducts	1 adenoca. 2 adenoca. of common duct			0	3
2	kidney	1 hypernephroma 1 adenoca.			0	2

CONTINUED ON NEXT PAGE

TABLE V—*Continued*

No. of Cases	*Site*	*Type*	*Regional Spread*	*Distant Spread*	*Test* —	+
2	thyroid	2 adenoca.		1 bone	0	2
2	larynx	2 adenoca.	2		0	2
2	brain	1 neuroglioma 1 glioblastoma			0	2
2	testicle	2 adenoca.	1		0	2
2	vulva	1 sarcoma 1 sq. cell carcinoma	2		0	2
2	bones	2 osteosarc.			0	2
1	penis	1 basal cell ca.			0	1
1	mediastinum	1 lymphosarc.			0	1
1	pleura	1 multiple sarc.			0	1
2	lower extremities	2 Kaposi's sarc.			0	2
2		multiple myeloma			1	1
8		chr. lymph. leukemia			1	7
1		aleukemic leukemia			0	1
6		Hodgkin's disease			1	5
6		generalized ca. 2 from ovary 2 from uterus 2 primary lesion unknown			0	6
8		metastases to liver 4 from stomach 2 from pancreas 2 primary lesion unknown			0	8
7		metastatic lymph nodes, 4 breast 3 primary site unknown			1	6
5		metastases to vertebrae from breast			0	5
3		metastases to brain 2 from lung 1 primary lesion unknown			1	2
6		3 lymphepithelioma 2 reticulum cell sarcoma 1 myxoleiomyo-sarcoma			1	5
357					30	327

TABLE VI—HEMOGLOBIN VALUES IN 212 CASES OF FRANK MALIGNANCY

Grams hgb. per 100 ml.	*No. of cases with negative reaction*	*No. of cases with positive reaction*
7 - 8	0	9
8 - 9	2	26
9 - 10	3	22
10 - 11	6	74
11 - 12	4	41
12 - 13	1	22
13 - 14	1	1

TABLE VII—TOTAL SERUM PROTEIN VALUES OF THE SAME 212 CASES AS IN TABLE VI

Grams total serum protein per 100 ml.	*No. of cases with negative reaction*	*No. of cases with positive reaction*
5.3 - 5.8	2	24
5.8 - 6.3	7	62
6.3 - 6.8	4	73
6.8 - 7.3	3	27
7.3 - 8.0	0	9
over 9.0	1	0

(*Discussion continued from page 702*)

albumin gave the negative reaction from 5 per cent concentration upwards, while with serum globulin a 10 per cent concentration was needed for a corresponding reaction. Results obtained with other proteins will be published later.

With human sera a total serum protein concentration below 5.3 per cent always resulted in a positive reaction, while in the few cases of hyperproteinemia, with values of above 9 per cent the reaction was invariably negative. Within these two threshold concentrations, no correlation has been found between the outcome of the reaction and the total protein content, or the ratio of albumin and globulin of the

serum (as determined by the conventional methods).

The appearance of the positive reaction below 5.3 per cent total serum protein is the consequence of a too low concentration of protein to form a firm enough structure to resist rapid penetration of the phenol into the inner parts of the drop. On the contrary, in total serum protein concentrations of above 9 per cent, no matter what other conditions co-exist in the serum, the reaction will always be negative; the high protein content and consequently, the extremely firm wall of the drop, impedes the rapid penetration of the phenol into the inner layers.

Within these two limits, either the positive or the negative reaction appears, depending upon the co-existing conditions of the highly complicated colloidal system of the serum. Such determining factors may be, among others: the varying relative and absolute amounts of the protein fractions; the amounts of lipoproteins and lipids; the molecular and ion concentration; the surface tension, the viscosity, and the hydrogen ion concentration.

Because the outcome of the reaction proved independent of the ratio of the albumin and globulin (as determined by conventional methods), an attempt was made to establish a different behavior of these fractions toward phenol. It was found that both in the aqueous phenol solution and the concentrated phenol, isolated globulin becomes denatured by the usual criteria of protein denaturation, while the albumin remains undenatured. It was also found that in some human sera the denatured and undenatured protein fractions differ quantitatively from the albumin and globulin, as determined by the conventional methods. Studies of these fractions in health and disease are now in progress.

Because of the lack of proper facilities, detailed studies were not made of other physico-chemical properties of the sera, as to the influence they may have on the reaction. The results of the few experiments conducted in this direction seem to indicate that to none of the chemical or physico-chemical properties of the serum by themselves can the formation of the two so distinctly different patterns be attributed, but rather that all, or the majority of the co-existent factors contribute to the appearance of the phenomenon. In other words: the positive and the negative reactions seem to be not the result of one single difference of the sera, whether in chemical composition or in physico-chemical properties, but rather the result of the difference between the sera in their entirety.

There are also other essential studies which have not been conducted. Among these are: the behavior of sera of animals with cancer; the methodical checking of the reversals of the test during treatment; the systematic selection of patients or groups of patients. Therefore, the study was limited to empiric clinical material. The connection between the outcome of the reaction as a probable indication of derangement of the protein metabolism, and the disturbed carbohydrate metabolism in diabetes should also be further investigated. Another potential field of investigation might well be research into the mechanism of the effect of certain drugs on the outcome of this test.*

How close the method reaches the criteria of a diagnostic test for cancer, so aptly defined by Homburger,[4] will be established only by the methodical observation of each available clinical case in a very large series. It is to be hoped that further investigations will rectify and complement the deficiencies and omissions of this study in both the theoretical and the clinical field.

ACKNOWLEDGMENTS

In the early stage of the study permission to use clinical material was given by the Jewish Hospital of Brooklyn and the Grace Clinic in Brooklyn. This help is acknowledged with thanks.

Gratitude is expressed for assistance rendered, and for the performing of the test in a number of series together with a study of the pertinent clinical data: to the Department of Obstetrics and Gynecology of the University Hospital of the New York University College of Medicine; to the Department of Chemistry of the New York University College of Medicine; to the 4th Medical Division of Bellevue Hospital, New York; and to the Methodist Hospital of Brooklyn.

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* The influence of administration of one of these drugs with sub-therapeutic doses has been applied recently to a procedure which may be called the "provocative test." 100,000 units of crystalline penicillin were administered to seventy-five apparently healthy individuals, and blood for the test was taken twenty-four hours later. In each, the reaction was negative. Five patients with proven cancer, in each of which the reaction was falsely negative, were also given the same dose of penicillin; twenty-four hours later, each reaction became positive. Further work with this phenomenon is being carried out at present at the Methodist Hospital of Brooklyn.

CLINICAL DISCUSSION — LOCKE L. MACKENZIE

It need hardly be said that the importance of any accurate test for cancer cannot be overemphasized. During recent years, a multitude of tests has been devised, but, for one reason or another, they have not been overly useful. The simple dicta that such a test must be inexpensive, accurate, easy to perform, reproducible, and, it should be added, that it must have a definite end point have not been satisfied by any procedure described as yet.

If such a test were to be devised it could be used in two ways. First, as a screening procedure for large segments of the population, and second, as a diagnostic aid. The former use would lend itself to clinics, including cancer detection clinics, and to routine office use, much as serological tests for syphilis are now used. As a diagnostic aid, such a test would be invaluable, much as the tests for pregnancy have proven to be. Still remaining would be the problem of finding the location of the malignant growth.

When the Sagi-Pless test was first brought to the University Hospital, the Department of Obstetrics and Gynecology was particularly interested in screening tests for cancer, and was engaged in a large scale evaluation of several such procedures. It was decided to run this test on 1,000 blood donors as a preliminary pilot study, and, if a number of positive reactions was found, no further work would be done with it. In this series, there were three positive tests. On repetition of two of these with fasting blood, one became negative, while the other remained positive. The third donor could not be found. Encouraged by this, further work was done during the next three years. Because of the fact that analyzable statistics have not yet been obtained, only a clinical impression is now available. In over 3,000 tests, there has been a reasonable correlation of accuracy. Before a preliminary report was presented, three small series were run independently at other institutions. In two of these, all work was done by the technicians and staff of the other hospital. In the third, sera were examined by one of the authors (E.S.) who knew nothing about the clinical diagnosis. These three series showed an accuracy of 92 per cent, 92.5 per cent and 96 per cent.

There are several zones, as has been indicated, in which this test quite regularly gives a positive reaction aside from malignancy. Fortunately, they are well recognized, and, for the most part, may be readily

diagnosed. It is possible that further laboratory work may reduce these areas, increasing the specificity of the test.

From the point of view of the public health, the implications of any test for cancer which is not 100 per cent accurate are somewhat hazardous. Even if such a test were 95 per cent accurate, and it were to be applied as a screening procedure to a large population, there might be 2 to 3 per cent of this population living in a sense of false security, while an equal number might be unduly concerned. This concern would assuredly be transferred to physicians also. In a large city, the number of false negatives and false positives would be very considerable.

Granting this serious objection to a cancer test not entirely accurate, it is still most important to find a test which is reasonably accurate, and strive to improve this accuracy.

The Sagi-Pless test seems to fulfill most of the desirable criteria of such a test. A well controlled clinical trial is absolutely necessary for proper evaluation. Such a trial should include very large numbers of patients, suffering from all types of disease and dysfunction. Both sexes and all age groups must be studied. Complete objectivity must be maintained, so that the technician has no idea of the clinical diagnosis. Such a regime is not easy to set up, and it is very difficult to administer, requiring the full time of trained investigators, the active cooperation of hospitals, as well as trained biostatisticians to evaluate the results.

This preliminary report describes, then, a test for malignancy, which appears to show promise. Its advantages seem to outweigh its disadvantages. Purely clinical impressions are that it is capable of detecting or ruling out the presence of cancer with a relatively high degree of accuracy. The implications of false negative and false positive tests have been discussed. Much work remains to be done, and this report has indicated some of the directions which might well be taken in the future to improve the procedure and to understand the mechanism of the phenomenon.

More than anything else, it may be a help in the early diagnosis of cancer. Until the etiology of malignant disease is discovered, its early diagnosis still will remain the most important single point of attack in its cure.

MEDICAL RESEARCH FORUM

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ABSTRACTS

"Vertical" Transmission of Leukemia

A Working Hypothesis on the Etiology of Leukemia and Allied Diseases

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Recent experiments suggest that mouse leukemia is caused by a filterable agent transmitted vertically, i.e., from one generation to another, directly through the embryos. In the high leukemic Ak and C58 inbred lines of mice, the leukemic agent may be associated with another oncogenic agent capable of producing salivary gland carcinomas in C3H mice. Both agents could be transmitted into C3H mice provided that newborn animals were used for inoculation. The injected animals remained in good health at first, but developed leukemia, or salivary gland tumors, after several months.

Although no experimental evidence is yet available concerning the nature of leukemia in humans, the possibility should be considered that, as in chickens and mice, in other species also, including humans, leukemia may be caused by a transmissible agent.

There may exist a group of submicroscopic oncogenic agents individually distinct (some causing leukemia, others causing different malignant tumors), transmitted directly, usually through the germinal cells, from one generation to another. These agents would exist in an inactive form, frugal and moderate in their requirements, causing no apparent harm to their carrier-hosts. Occasionally, however, prompted by as yet obscure, but presumably varied, trigger stimuli, these hitherto masked agents may change into formidable pathogens. Activated oncogenic agents would cause rapid multiplication of cells harboring them, resulting in leukemia, or another malignant new growth.

Actually, the development of either leukemia or that of another malignant tumor would be the cumulative result of the following four essential conditions: 1) Susceptibility of host (inherited, genetic); 2) presence (usually since host's birth) of an oncogenic agent potentially pathogenic for its carrier-host; 3) trigger shock, ultimately responsible for the induction of the tumor. The trigger could be intrinsic (possibly metabolic, or hormonal) or extrinsic (physical, or chemical); 4) proper conditioning of the host (hormonal, nutritional and environmental) permitting the trigger shock to activate the tumor agent (starvation, for example, could prevent activation of tumor agent; hormonal stimulation could prompt, or prevent, induction of certain tumors, etc.).

Since in many instances the oncogenic agents would never become activated, only now and then leukemia, or other malignant tumors, would develop in some of the members of such families that carry and transmit the agents. Such instances, however, may be separated by one, or several generations of healthy individuals. It would then have to be assumed that the number of individuals suffering from tumors or leukemia would represent only a fraction of those actually carrying the seeds of either disease.

*The Nickerson-Kveim Reaction in Sarcoidosis**

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The Nickerson-Kveim cutaneous test for sarcoidosis as employed in our studies consisted of the intradermal injection of a heat-sterilized suspension of human sarcoid tissue and the subsequent histologic examination of the site of injection. In a positive reaction a sarcoid-like granuloma is produced at the injection site after some weeks.

The test was given to 200 patients. Fifty-eight patients had sarcoidosis, the diagnosis being confirmed by biopsy of an involved organ or tissue. Eighty were sarcoidosis suspects; of these, thirty-three were strong suspects. Fifty-four patients had diseases other than sarcoidosis, and they served as "controls." Eight patients had unclassified granulomatous disorders.

Results of this study disclose that a high percentage of the biopsy-confirmed group and of the group containing strong suspects had histologically positive responses to the test—86 per cent of the former and 85 per cent of the latter.

Two patients in the "control" group had positive responses to the test, an incidence of 4 per cent of false positive reactions.

Biopsy of the injection site was considered an obligatory part of the intracutaneous test in this study. The biopsies were usually carried out four to six weeks after the sarcoid suspensions were injected. In all, 571 biopsies of Nickerson-Kveim test areas were performed.

In this study a Nickerson-Kveim result was called positive only if a histologically characteristic sarcoid-like granuloma could be demonstrated at the site of injection after a suitable interval.

Foreign body reactions and non-specific reactions sometimes interfered with the microscopic reading of the test.

Suspensions of normal lymph node and normal spleen did not evoke a positive reaction in patients having sarcoidosis, who did respond to a suspension of sarcoid tissue.

The Nickerson-Kveim intracutaneous test is a useful confirmatory tool in the diagnosis of sarcoidosis. The test is of aid especially when tissue from involved organs is not readily accessible to biopsy.

The test has growing applicability in the fields of internal medicine, ophthalmology and dermatology where problems in differentiating granulomatous conditions often arise. In such instances the result of the Nickerson-Kveim reaction can also be a determining factor in the choice of proper therapy.

* Support for this study was received from the General Research Fund of The Mount Sinai Hospital and from the Aaron W. Davis Foundation.

TABLE 1—RESULTS OF THE NICKERSON-KVEIM TEST IN 200 PATIENTS; 571 TEST AREAS BIOPSIED

Patient-Group	*Number in Specified Group*	*Positive Tests*		*Number of Test Areas Biopsied*
		Number of Patients	*Per Cent*	
1. Biopsy-Confirmed Sarcoidosis	58	50	86	198
2. Sarcoidosis Suspects	80	41	51	231
Strong	33	28	85	
Intermediate	24	12	50	
Weak	23	1	4	
3. Other Diseases, Controls	54	2	4	112
4. Unclassified	8	3	—	30

The Artificial Uterus and the Passage of Radioactive Sodium Through Hemochorial Mammalian Placenta Extra Utero

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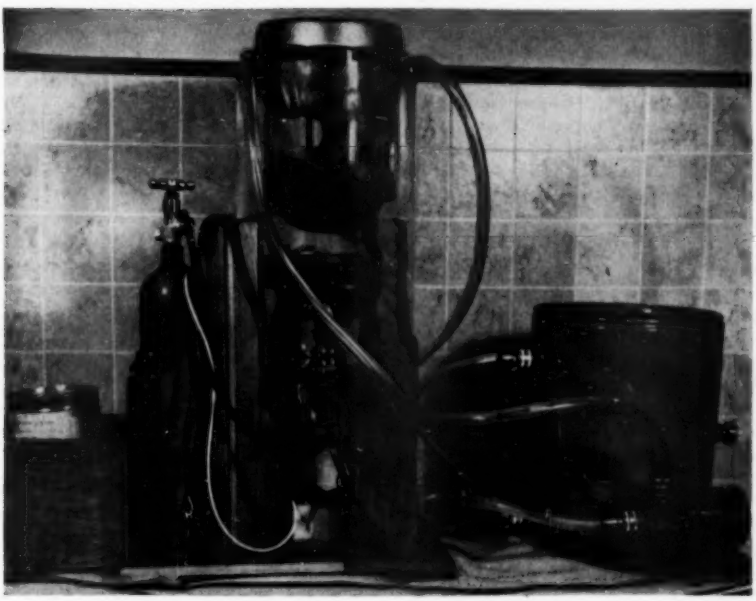

Figure 1

The construction of a working model for a life-size, artificial uterus is herewith reported and demonstrated (Fig. 1).

The purpose of the artificial uterus is to salvage those prematurely passed fetuses which are too young to survive in an extra-uterine environment. By not cutting the umbilical cord, the integrity of the "FCP" (Fetus, Cord and Placenta) as one unit is maintained; the placenta is immersed in a blood chamber known as the placental lake, whence the placenta absorbs oxygen, from oxygenated blood, and nutrients, and gives off waste products. The placental lake is connected to an artificial heart,—lung and artificial kidney. Bacteriological sterility, constant temperature control, and essential nutrients are provided.[1]

The following experiment was performed in the course of the author's investigations on the artificial uterus. It demonstrates the ability of the placenta and umbilical cord system to permit ionic absorption and transfer to the embryo extra-utero. This experi-

ment lends strong support to the physiological validity of the artificial uterus.

A white rat, in the seventeenth day of gestation, was cesareanized under intraperitoneal barbiturate anesthesia. The embryos were delivered by careful hysterotomy followed by a delicate expression from the uterus; in the process of "shelling out" the embryos, care was taken not to rupture the amniotic sac. (The author will refer to this as "amnio-cesarean section.")

The technique of amnio-cesarean section was finally mastered so that embryos could be removed with comparative ease without rupturing the amniotic sac. The placentas (which are close to the embryo when the latter is removed with amnion intact) were immersed in a lake of radioactive sodium in a watch glass for five minutes. The placentas were cut off, and the embryos were then exposed to the Geiger counter. An appreciable amount of radioactivity was demonstrated to be present in the fetus; this was substantially greater than the amount of background radioactivity in the room.

The passage of the sodium ion through the placental capillaries and the umbilical vein to the body of the fetus itself is to be inferred, and illustrates one of the component mechanisms upon which the function of the artificial uterus depends.

It was then decided to discard the obstetrical technique of amnio-section and to perform a classical cesarean section, deliberately cutting the amniotic sac. The purpose of this was to permit the placenta to become separated from its embryo by the length of its cord, so that the distance of the full length of the cord would separate the lake of radioactive sodium and its immersed placenta from the embryo.

The experiment was thus repeated, with placenta separated from fetus by full cord length, and following a five minute period of immersion of the placenta in the lake of radioactive sodium, the umbilical cord was severed close to the embryo, separating the latter from both cord and placenta. Care was taken to prevent contamination of the body of the embryo with the radioactive lake. The embryo was then washed as an added precaution.

Geiger counter readings were again indicative of appreciable and significant absorption of the radioactive sodium.

This procedure was repeatedly confirmatory in sixteen cases. While the transplacental passage and fetal absorption of Na ions is well known in utero,[2] it has not previously been demonstrated extra-utero. Extra-uterine transplacental ionic passage is an additional support to the physiologic validity of an artificial uterus.

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Theoretical Considerations of Enzymes in Uremia

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Diminution of renal reserve sufficient to effect oliguria and inadequate excretion of nitrogenous catabolites defines the uremic state. No "toxin" has been biochemically identified as etiologic for this state. Anatomical damage of the kidney need not be present; functional inadequacy secondary to extra-renal insult accomplishes the same adverse result.[1] The latter situation is termed pre-renal azotemia.

Informed guesses as to the chemical nature of the "uremic agent" would suggest, on the one hand, a protein-like complex of high molecular weight[2] in that it cannot pass through the glomerular membrane. Conversely, substances of low molecular weight have been postulated as the offending factors in uremia in that they may be removed by extracorporeal dialysis.[3] In any case, it is unknown whether the "toxin" preexists the development of renal failure or forms during the period of impaired renal function.[4] The partition-fraction within the plasma of this "uremic agent" has not been characterized;[5] however, globulin is relatively increased in the hypoproteinemia of uremia.[6] Neither urea, (alternately regarded as an innocuous[5, 7] and toxic[8] catabolite), nor any specific amino acids, nor combinations of such moieties, given orally or parenterally, will produce complete uremia.[7] No correlation can be made between symptom-severity and elevated serum levels of urea nitrogen, phenol, guanidine and creatinine in uremia.[9]

In an effort to evaluate enzymatic relationships in an investigative or therapeutic attack upon uremia, several problems are encountered. First, it is questionable that any parenterally administered enzyme used to date achieves proper absorption into the cell where its action is proximately sought. However, elevated plasma levels of certain reaction products formed by some enzyme-substrate systems have been recorded in animals following subcutaneous injection of the enzyme.[10] Successful alteration of transcapillary exchange of K^{42} by use of intravenous hyaluronidase has been reported.[11] Finally, the rapid liberation of toxic products following at least one type of enzyme reaction in vivo (viz., urease given intravenously, releasing ammonia), may produce sudden death of the animal.[12] As a further complication attending parenteral administration of enzyme, immunological problems arise with the repeated use of any of these foreign protein complexes.[13-15]

Urea is removed from the plasma by glomerular filtration and tubular back-diffusion. However, a persistent increase in blood urea nitrogen beyond the augmentation limit, withstanding rapid urinary excretion by profound diuresis,[16] should theoretically be made possible by surgical ablation of much of an animal's renal parenchyma.[17] Parenterally administered arginine or glutamine might bring about elevated blood urea nitrogen in the presence of such renal depletion if the urea formed by the action of arginase in the ornithine cycle,[18] or ammonia formed through mediation of glutaminase and then glutamic acid dehydrogenase[19] could be re-incorporated into either cycle. Of course, further insult to the remaining parenchyma in such an animal, in the form of drug-induced ganglionic blockade,[20] hemorrhage,[21] or chronic anemia,[4] could lead to uremia, but the cause-and-effect relationship of amino acid and enzyme reaction in experimental control of uremia would thus be somewhat obfuscated. It may well be that the kidney is simply the target-organ for extensive multiple systemic disorders involved in uremia rather than the

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seat of enzyme production, activation or deactivation, roughly analogous to the VEM mechanism in hemorrhagic shock postulated by Zweifach.[22]

Coordination of several disciplines is required to assay enzyme-control mechanisms in renal failure. Biochemical analysis of protein metabolism, physiological determination of cellular site of enzyme action, immunological estimation of antibody obstruction to protracted use of parenterally administered enzymes and clinical identification of modalities producing the given uremic state must dovetail in order to evaluate and adjust the disturbed homeostasis.

No comprehensive research scheme is proffered. Careful, thoroughgoing attack, utilizing fairly narrow media within one or several of the cognate scientific branches, should offer promise of producing much-needed information. Several investigative pathways are discussed.

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Scintillation Measurements of the Uptake of Radioactive Vitamin B_{12} by the Liver in Normal Humans and Patients with Pernicious and Other Macrocytic Anemias[*]

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The metabolic turn-over of radioactive vitamin B_{12} injected or given orally to forty normal individuals, and patients with various diseases including pernicious and other macrocytic anemias was studied by scintillation counting of radioactivity over various skin projections of underlying organs with special emphasis upon the liver. Over 4300 individual surface counts were taken during the observation periods ranging from five days to eight months and a procedure was developed for the measurement of the hepatic uptake of radioactive vitamin B_{12} in humans. The tracer doses were used which were much below the maximum permissible amounts of radioactive Co^{60} for use in humans. The results obtained indicate that this method can be applied to the study of metabolism of vitamin B_{12} in humans under normal and pathological conditions, as successfully as the counting of radioactive I^{131} over the thyroid is applied to the study of the metabolism of iodine and thyroid hormone, provided that adequate doses, timing and controls are used.

Following the intramuscular injection of 5-10 mcg. radioactive vitamin B_{12} about 95 per cent of the injected material disappears from the site of the injection within two hours, and at the end of that time the radioactivity rises to the peak values over the areas corresponding to kidneys, spleen, iliac crest and somewhat later over extremities. It required from four to six days, however, to build up the peak of radioactivity over the liver. The counts built up over the liver exceeded several times those over the kidneys and other areas of the body, and the decline of radioactivity over the liver was slower than over the other organs and amounted to only about 14 per cent of the peak value at the end of two to three months. The patterns of the hepatic uptake of radioactive vitamin B_{12} following its parenteral administration were grossly similar in patients with total gastrectomy and pernicious anemia to those observed in normals, with a somewhat faster building up of radioactivity over the liver and other visceral organs, and slightly faster decline of the radioactivity over these organs during the course of study.

The long storage period of radioactive vitamin B_{12} in the liver may explain the long period of remission in pernicious anemia following successful treatment with liver extracts or vitamin B_{12}, and a long period of time necessary to deplete the stores of vitamin B_{12} under normal conditions, and to develop a macrocytic anemia after total gastrectomy.

The effect of oral administration of various doses of radioactive vitamin B_{12} (0.5-50 mcg. containing from 0.1 to 2.0 mcc. Co^{60}) was studied on forty individuals. The ingestion of radioactive vitamin B_{12} results in the accumulation of the radioactive material in the upper left abdomen immediately following ingestion. This shifts to the mid- and lower abdomen during the next twenty-four hours. Starting with the second to third day the average counts over the entire abdomen decrease rapidly, and usually within six to eight days the counts over the mid- and lower abdomen fall to a minimum in individuals with a normal bowel function (after cathartics—in patients with severe constipation).

The only abdominal area showing progressive rise in radioactivity up to the sixth to fourteenth day under these circumstances was the liver, the counts over which in

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[†] With technical assistance of Gerald A. Gellin, Loukia Stephanson and Everett L. Jones.

TABLE I—MEASUREMENT OF THE HEPATIC UPTAKE OF RADIOACTIVE VITAMIN B_{12} VS. CLASSICAL METHOD OF HEMATOPOIETIC RESPONSES IN THE ASSAY OF INTRINSIC FACTOR PREPARATIONS*

Preparation and dose	*Hepatic uptake of radioactive B_{12} in counts per minute above background*	*Hematopoietic responses on patients with pernicious anemia in relapse*
I-M-31 1 mg.	0 (case P. M.)	*Not active* in a daily dose of 1 mg. on 3 patients, and 10 mg. on 1 patient.
I-M-31 9 mg.	0 (case P. M.)	
62301 39.8 mg.	64 (case P. M.)	*Highly active* in a daily dose of 39.8 mg. on 3 patients.
63301 41.6 mg.	50 (case P. M.)	*Highly active* in a daily dose of 41.6 mg. on 3 patients.
63301 41.6 mg.	44 (case W. B.)	
63301 58.0 mg.	78 (case W. B.)	
63301 58.0 mg.	100 (case P. M.)	
63301 116.0 mg.	109 (case A. S.)	
64301 40.0 mg.	0 (case A. S.)	*Not active* in a daily dose of 16.0-40.0 mg. on 6 patients.
65301 40.0 mg.	0 (case P. M.)	*Not active*—same results as with preparation 64301.

normal individuals, as well as in patients with various diseases, exceeded up to four times those over the rest of the abdomen. This difference was statistically highly significant, the "p" value being below 0.05. In all six patients with pernicious anemia studied in relapse or remission, the hepatic uptake of the ingested radioactive vitamin B_{12} was nil or negligible; however, it became normal after the same dose of radioactive vitamin B_{12} was given orally either together with 75-95 cc. of normal human gastric juice or with a potent source of intrinsic factor from hog gastric mucosa. In a case of sprue, the uptake of the ingested vitamin B_{12} by the liver was also nil, but it did not change after the addition of the normal gastric juice or intrinsic factor concentrate from hog stomach. In nutritional and hemolytic anemias with unimpaired gastric secretion the uptake of the ingested radioactive vitamin B_{12} by the liver was on a normal level.

The scintillation measurement of the hepatic uptake of radioactive vitamin B_{12} following oral administration of 1-2 mcg. Co^{60} containing vitamin B_{12} of high specific activity alone and with intrinsic factor containing material, is proposed, as a test for evaluation of the intestinal absorption of vitamin B_{12} in humans as well as for the assay of the intrinsic factor activity of various materials processed from human or animal sources.

The reliability of this method of measurement of intrinsic factor activity was confirmed by results of comparative assays of several batches of intrinsic factor concentrates from hog stomach which were tested with classical method of reticulocyte and red cell responses on patients with pernicious anemia in relapse and independently with our isotope technique on patients with pernicious anemia in remission. The hematological assays were done by other investigators without our knowledge of results obtained and preparations we studied were marked only by numbers.* A complete concordance of results was obtained, as shown by Table I. Preparations which were highly active in hematological study promoted positive uptake of radioactive vitamin B_{12} as measured by our technique, and conversely, these preparations which were inactive on hematological assay did not show any hepatic uptake of radioactive B_{12} in our study.

* These preparations were obtained through the courtesy of Dr. K. W. Thompson, Vice-President, Organon Inc., who also kindly supplied the data on hematopoietic responses obtained with preparations listed in Table I.

*Newer Clinical and Laboratory Studies in the Aged: II: Correlated Serum Lipid Partitions and Lipoprotein Molecules (Sf 0-400) In Patients 80-100 Years of Age: Preliminary Report**

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There have been no published studies to date, of serum lipid partitions, ultracentrifuge lipoprotein fractions and their interrelationships with clinical data, electrophoretic patterns, x-ray and pathological findings in the eighty to one hundred year group. Seventy-five such patients with no known past histories of metabolic or coronary artery disease, confined to Bird S. Coler Memorial Hospital were studied.

Total serum lipid mean averages are considerably lower in this age group than in the normal and atherosclerotic individuals.[1-3] There was no significant difference in the serum total cholesterol nor phospholipid levels. Compared to the younger age group, the phospholipid to total cholesterol ratio (P/C ratio) was less than 1.00 due to the higher values for total cholesterol and lower values for phospholipids.[4]

There was a considerable decline in the standard Sf 0-12, Sf 12-400 lipoprotein fractions and the atherogenic index in the older age group.

Total serum lipids, standard Sf lipoprotein molecule values and the atherogenic index rise steadily, in both males and females from age twenty until approximately age sixty-five and seventy-five years,[5, 6] after which there is a steady decline until age one hundred years. There seems to be a "threshold" between the ages of approximately sixty-five and seventy-five years after which there is a decline of total serum lipids, lipoproteins and atherogenic index. Cholesterol and phospholipids show no significant changes.

There does not appear to be a close relationship between the ratio of alpha to beta lipoproteins obtained by paper electrophoresis, using Oil Red O, and the Sf lipoprotein values obtained on the same sera by the ultra analytical centrifuge method.

Two hundred and fifty routine chest films were surveyed for calcification of the thoracic aorta, including the seventy-five patients of this series. In the sixty-eighty age group, 37 per cent males and 54 per cent females had calcification. In the eighty to one hundred year age group, 58 per cent males and 87 per cent females revealed evidence of calcification. The percentage of calcification of the thoracic aorta increases with age.

Postmortem examinations of tissues obtained from patients of this series including cross sections of the aorta at various levels show close correlations with x-ray studies. The demonstrated changes are as anticipated in older age groups.

Low standard Sf lipoprotein values and low atherogenic index values were obtained in the eighty to one hundred year age group. The same patients showed marked x-ray thoracic calcification and increased histological atherosclerosis as well as clinical evidence of atherosclerosis.

Eighty to one hundred year old patients show marked x-ray thoracic calcification and microscopic atherosclerosis, although they have a low atherogenic index and low Sf 0-12 and Sf 12-400 lipoprotein molecule values.

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Serum Lipoproteins in Newborns and Infants

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This study was undertaken to ascertain the serum lipoproteins as measured by ultracentrifugation in newborn infants before their first feeding, on their second and fifth day of life, and at the age of one month. Both sexes were studied, as well as the bloods of the mothers and placental bloods.

Lipoproteins in the class of Sf 0-12, Sf 12-20 and Sf 20-100 were determined, using standard techniques. Table I is a preliminary report of the findings:

Apparently, newer density lipoproteins appear as the newborn ages, and the food intake increases. Because true function of the adrenal cortex begins at about the fifth day of life in humans, some effect on elaborations of the macromolecules may be due to this event.

In the newborn, before the first feeding, six cases were studied. In the two-day olds, four cases, and in the five-day olds, five subjects were used. The one month of age infants represent a group of eleven infants.

Placental bloods are almost free of these classes of lipoproteins, and the mothers' blood levels bear no relation to the levels in the newborn in the thirteen infants studied.

TABLE I—LIPOPROTEINS IN NEWBORN

Class of Lipoproteins	*Age of Infant in Days*			
	0	2	5	30
Sf 0-12	68	97	126	101
Sf 12-20	0	3	7	9
Sf 20-100	0	5	8	13

NEW YORK PATHOLOGICAL SOCIETY

and the

SECTION ON OPHTHALMOLOGY

Abstracts of Papers and Discussion

Presented at the Meeting, December 21, 1953, at The New York Academy of Medicine

Malignant Lymphoma with Ocular Involvement: Clinicopathologic Report

ISADORE GIVNER

A female, married, age forty-nine, presented herself December 10, 1951 with a history of having had an acute pancreatitis three months previously, at which time the vision of the left eye was affected. Since that time the vision of the right eye is also not clear.

Ophthalmologic examination: The right eye showed a nongranulomatous uveitis. The vision was still 20/20-. The left eye was normal, except for the vision, which was 20/200, and an elevated mass in the macular area. With it was some subretinal fluid and three smaller lesions below the main one. The lesion transilluminated well.

The complete examination of the patient was negative. Subconjunctival injections of cortisone produced no change in the right eye, but the appearance of the left macula was markedly altered. The lesion disappeared, leaving pigmented degenerative areas. The vision improved gradually until May 16, 1952 when the vision was 20/25-.

The patient was concerned about her right eye and asked for a consultation with Dr. Alan C. Woods. His examination showed no general condition other than a three plus reaction to one out of 28 strains of subgroup A of the beta hemolytic streptococcus. He advised intravenous desensitization. This was begun June 20, 1952, 1/10 cc. of first strength vaccine being given. The following day styes appeared on the lids of both eyes. One week later a swelling of the left parotid gland occurred. Biopsy showed inflammatory tissue. At this time all the glands over the body were enlarged. After x-ray treatments the left parotid area returned to normal. As the patient felt there was some connection between the intravenous vaccine and her general condition, no further intravenous streptococcic vaccines were given.

On September 28, 1952 the patient developed a weakness of her left arm, a left facial paralysis and ptosis of the right upper lid associated with stupor. She was operated on and a brain tumor was found in the left tempero-parietal region, so that the neurologic findings must have been due to the distant effects of pressure. The undifferentiated malignant growth removed resembled reticulum cell sarcoma. The patient did not do well until given intravenous nitrogen mustard 8 mg. daily. Remarkable improvement then occurred and the patient

later walked out of the hospital feeling well.

On December 17, 1952 metastatic lesions occurred in the bulbar conjunctiva of both eyes as well as in the skin of the chest. Biopsy showed reticulum cell sarcoma.

At this point the thought as to whether the streptococcus vaccine could have hastened the generalized involvement called for clarification. That the streptococcus has been linked to lymphosarcoma is attested to by the history of Coley's vaccine. Busch[1] in 1868 noticed that lymphosarcoma occasionally disappeared if the patient contracted erysipelas. In 1881 Fehleisen[2] discovered the Streptococcus erysipelatis and inoculated human patients with this culture to make lymphosarcoma regress.

William B. Coley[3] at New York Hospital in 1884 noted ten cases of lymphosarcoma which permanently disappeared after acquiring erysipelas. In 1891 he tried killed cultures of Streptococcus erysipelatis, but these preparations were too weak. In 1892 he utilized a fact uncovered by Roger[4] at the Pasteur Institute that B. prodigiosus increased the virulence of other organisms and used Coley's mixed toxins of both the streptococcus erysipelatis and B. prodigiosus.

Bradley L. Coley, the son of William B. Coley, today finds that 50 per cent of patients with reticulum cell sarcoma treated with irradiation and Coley's vaccine are alive after five years. In one case cited in his book "Neoplasms of Bone," a patient with this condition who had already had metastasis to the spine, scalp and clavicle was well twenty-one years later, having been treated only with the Coley's vaccine.[5]

A piece of biopsied tissue from the skin in the case presented this evening was placed in the anterior chamber of a rabbit, but did not grow. This lack of growth of malignant lymphoma was also the experience of Dr. Harry S. N. Greene[6] of Yale who initiated this type of experimentation to help differentiate anaplastic tissue. The tissue did not grow even after the rabbit was given intravenous streptococcus vaccine of the strain to which the patient was sensitive. Nitrogen mustard again caused the disappearance of the patient's lesions.

The course was now downhill. The vitreous of the right eye became more cloudy. The left eye developed a subconjunctival salmon-colored chemosis. The patient died May 19, 1953. Permission for complete autopsy including examination of both globes was procured. The vitreous of the right eye showed many inflammatory cells,—polymorphonuclear leukocytes, lymphocytes and plasma cells,—but in the region of the ciliary body the vitreous in all serial sections made showed cells that were well preserved, with larger nuclei than in the other cells of the vitreous.

In the left eye there was a marked subconjunctival infiltration of lymphomatous cells invading the superficial sclera and extending onto the cornea. The macula of the left eye showed subretinal transudate and a marked thickening (six times the normal) of the lamina vitrea, suggestive of a degenerative lesion.

Subsequent skin testing of two other patients with generalized lymphosarcoma showed no sensitivity to the vaccine to which the patient in question was sensitive.

Conclusion: Any relationship that might seem to exist between the injection of the streptococcus vaccine and the precipitation of the reticulum cell sarcoma was purely coincidental.

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Lymphomatous Tumors of the Eye

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This paper is concerned with a follow-up of twenty of twenty-one patients with lymphomatous tumors involving the eye and its adnexa. In June 1942 a report of these patients was given at the A. M. A. meeting after an average follow-up of four years.[1] This second report gives a follow-up of fifteen years. In each case there was biopsy material from the ocular lesion as well as from any remote tumor.

Emphasis is placed on the fact that the lymphomatoid diseases are interrelated and transitional from one type to another, with or without leukemia.

Of the twenty patients, five are alive today and only one has evidence of disease. Five patients died of conditions other than lymphomas after an average of 15.5 years. Fourteen of the tumors were primary in the region of the eye and seven remained localized until 1953 or until death from other causes. The seven patients with tumors primary in the region of the eye which later spread, survived an average of 9.8 years, while those with generalized lymphosarcoma before an ocular tumor appeared survived only 4.6 years. The survival rates according to types were as follows: lymphocytic 13.6 years, giant follicle 13.0 years, reticulum cell 7.2 years.

It was found that the clinical appearance of the eye was the same for those who lived and for those who died. The histologic appearance of the subconjunctival tumors was not reliable for prognostic purposes. In general the prognosis is better than is generally believed.

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DISCUSSION

GEORGE R. MERRIAM: It is a pleasure and a privilege to discuss Dr. McGavic's paper. This is an unusual collection of cases that has been so ably presented that I wish to emphasize only a few important points and briefly discuss treatment.

Follow-up: One of the outstanding features of this series is the length of the follow-up. It is well known by those interested in the cancer problem that the number of survivors decreases with each five-year period of observation. It is this fact that makes a regular follow-up program of a single group such as this of such vital importance if we are to learn the true nature of this or any similar disease. The tendency for the disease to start as a localized process and later become generalized is appreciated only after such long term observation. It is this also which makes it impossible to speak of cures when reporting a series of patients with carcinoma. Rather one can speak only of survivors living with or free of disease for a given period. In reporting deaths it must be stated whether the patient died of the disease or from other causes with or without known residue of the original disease.

Biopsy: Another important feature of Dr. McGavic's series is the fact that all of the lesions were biopsied. This is essential for diagnosis, classification and for the planning and evaluation of therapy. It is to be urged that all tumors, no matter how typical they may appear clinically, be biopsied, for the only truly valid series are those in which microscopic examinations have been done. As new sites of involvement appear these too must be biopsied, for lymphomas may vary in type from site to site. Biopsy affords the only true means

for studying the course of the disease.

During the past six years we have treated at the Institute of Ophthalmology thirty-two patients with various types of ocular lymphosarcoma. Twelve were males and twenty females, with an average age of fifty-nine years. The disease was located in the orbit in twenty-three cases, of which four were primarily in the lacrimal gland, in the subconjunctival tissues in seven cases, in the lid in one case, and in the lacrimal sac in two instances. Biopsies were done on all patients and the pathologic diagnosis was lymphocytic cell type in fourteen and reticulum cell in twelve; in the remainder no cellular diagnosis was made. In fourteen of the patients the ocular involvement was only part of a generalized process. In eighteen cases there was no other evidence of the disease. The period of observation runs from two months to six and one-half years with an average of 27.3 months. This is too brief to allow one to draw conclusions. However, in this period three have died of their disease and eight are known to be living with disease. In all of these patients the ocular involvement was only part of a generalized process. None of the patients presenting ocular lymphosarcoma alone has as yet developed other manifestations of the disease. It is certain, however, that further observation will alter this situation.

Treatment: The excellent response of these lesions to irradiation is well known and requires no discussion. The main concern with the ocular tumors is the protection of the uninvolved structures. When only the lid is involved the eye can be shielded without difficulty. The lantern slides shown illustrate the treatment of tumors of the lid, conjunctiva, and orbit, giving the irradiation factors, and the appearance of the patients before and after treatment. When the neoplasm involves the subconjunctival tissues the problem of protecting the uninvolved portion of the eye becomes more difficult. A plaster cast was made of the patient's face and on this a lead shield was molded. The exact type of cut-out and the direction of the patient's gaze will vary depending upon the area to be treated. None of the patients has to date shown any evidence of radiation injury to the globe with the dosages and the shielding employed. The diagnoses of the tumors treated were lymphosarcoma, reticulum cell type, left upper eyelid; lymphocytic cell lymphosarcoma involving the left nasal bulbar conjunctiva (this patient had received 30 mg. of TEM [triethylene melamine, a form of nitrogen mustard] in divided doses), and lymphoma of orbit, lymphocytic cell type, two cases. The incidence of orbital involvement in our cases is considerably higher than in other series. They are, however, amenable to therapy provided the globe is adequately shielded. Whether this tumor is more prevalent than formerly, or whether we are more aware of it, is unknown. However, according to Dr. A. B. Reese, lymphomas now rank second to hemangiomas as the cause of exophthalmos in the pathologic files of the Institute of Ophthalmology in New York. The response to therapy in the two cases of lymphoma of the orbit of which slides were shown has been prompt and gratifying. One of the patients has been followed for eight and the other for two months and both are free of disease at present.

Dr. McGavic has made an outstanding contribution to our understanding of lymphosarcoma, not only as it affects various ocular structures, but in its relationship to the generalized process. I would again urge you to insist upon a biopsy and to follow your patients indefinitely whenever possible. Irradiation is the treatment of choice and with adequate protection a satisfactory response can be anticipated.

HENRY D. DIAMOND: I think we can re-emphasize some of the points brought out both in Dr. McGavic's paper and in the discussion by Dr. Merriam. In the first place, about 7 per cent of all recordable cancer does fall in the region of the lymphoma and leukemia grouping. As you probably realize, as in all cancer, the most effective period of time in which treatment can be instituted is in the early or localized phase of the disease, and I can restate a second fact that Dr. McGavic brought out, and that is that not infrequently any of the particular histologic varieties such as

Hodgkin's disease, in the categories of paragranuloma, granuloma, or sarcoma and lymphosarcoma, beginning with giant follicle lymphoma, going all the way down through diffuse lymphosarcoma and reticulum cell sarcoma, can be unicentric in origin. It is a well known clinical observation that these diseases in time tend to disseminate, so that actually in our treatment of the disease we should attempt to make a clinical classification and assessment of the patient at the first observation of the case in terms of the category I, II, or III: first, class I, those which fall into the category of unicentricity, without blood or other changes; or class II, early beginning generalization, though still regional localization of the disease; and finally the third category, class III, which is the universal category into which all patients with leukemia will obviously fall. I would hold indeed that the treatment of choice in all the varieties of lymphoma would be that of radiation therapy, certainly in category I, where theoretically, at least, cure is a possibility with adequate obliterative radiation therapy. All too often the clinician tends to treat, just to the point of disappearance of diseased tissue, even in patients who have unicentric or monofocal disease, without, therefore, giving the patient a chance of at least sterilization of the particular focus and long survival. I make this statement because in clinics where large numbers of lymphomas are seen, the patients who fall into the early unicentric group are the ones who go on to have the largest five-year survival rate. At one time the theory was promulgated that perhaps the survival rate could be assessed from the point of view of the microscopic appearance of the tumor, to which Dr. McGavic made reference. I do not, however, believe this can be correlated with the clinical aspect, since in certain instances, irrespective of the type of disease, or irrespective of the nature of treatment, long survival has occurred, but more often than not, irrespective again of the particular histologic nature of the tissue, if it is still localized to a single focus, adequate irradiation therapy may well produce long survival of the patient.

No reference tonight has been made to some of the chemical agents used in the treatment of this group, except nitrogen mustard. As you realize, there is a great field today in all of cancer, which is developing progressively, having to do with the chemotherapy of cancer, and this discipline plays an important role in the study and treatment of lymphomas. It is in lymphomas and leukemias that the testing of chemotherapeutic agents can be done most successfully, because there is material at hand to be biopsied at all times, and the normal evolution of the disease can be studied with reference to the effect of a chemotherapeutic agent. Reference was made by Dr. Merriam to triethylene melamine, a nitrogen mustard-like compound by virtue of its ethylene-imine moieties. Its value is that it is given orally in contradistinction to nitrogen mustard, which must be given intravenously. In the leukemias we have another fruitful testing ground for chemotherapeutic agents. Here we have agents which are the antagonists of normal metabolic functions themselves, and so can be used successfully in acute leukemia. These agents are essentially the antagonists of purine or folic acid. Cortisone and ACTH, which influence the hormonal environment of the cell, have been tried successfully. The eye from my point of view is no different from any other part of the body with lymphoma, since lymphomas can occur anywhere in the body.

I have said little specifically about Dr. McGavic's paper since I feel as an internist that I am not qualified to say much about the eye *per se* in the way Dr. McGavic and Dr. Merriam have. Certainly the paper is extremely interesting. I can only emphasize here that treatment should be that of aggressiveness, because long survival can and has been achieved in patients who have localized disease. I think Dr. McGavic and Dr. Merriam should be complimented for an interesting discussion tonight.

The Eye and Orbit in Trichinosis

S. E. GOULD

Department of Pathology, Wayne County General Hospital, Eloise, Michigan; Wayne University College of Medicine, Detroit, and University of Michigan, Ann Arbor, Michigan

Inasmuch as the ophthalmologist may be consulted early in trichinosis, often as the first physician, it is important that he be familiar with the ocular manifestations of the disease. These manifestations are chiefly the result of invasion by the larvae of Trichinella spiralis of the extraocular muscles, their development and encystment in the muscles, and of accompanying edema and inflammation in the muscles and adjacent ocular structures. Common symptoms, often occurring early, include edema of the eyelids and conjunctivae, frontal or supraorbital headache, conjunctivitis, hemorrhage in the orbital conjunctiva and pain on movement of the eyeballs. Of frequent occurrence also are retinal edema, hyperemia and short linear hemorrhages. In an epidemic of trichinosis involving sixty soldiers, reported by Schmidt,[1] linear retinal hemorrhages were seen rarely in mild infections (two of twenty-four), but in the majority of those with severe infestations (twenty-one of thirty-six); in twelve of fifteen patients who died, such hemorrhages were seen during life. Their clinical detection, therefore, may be regarded as of prognostic value.

In the literature only two instances have been encountered in which a human eye has been microscopically studied in fatal trichinosis. One of these (reported by Schmidt) showed iron deposits in the retina, which were believed to have been related to small retinal hemorrhages seen during life. The other instance (reported by von Herrenschwand[2]) showed conjunctivitis, heavy trichinous myositis of the extraocular muscles, minute retinal hemorrhages, and focal retinitis, and within six of ten focal inflammatory areas in the retina, a young trichina larva.

In an experimental study, we fed four rabbits and thirteen white rats heavy or lethal doses of trichina larvae, and histologically examined the ocular structures at various intervals up to thirty-three days, after feeding.

In rats that died at two days from diarrhea, extreme dehydration was reflected in the ocular apparatus by drying of the secretions in the conjunctival sacs, and by precipitation of the secretion of the lacrimal glands as seen in sections. Edema of the eyelids and conjunctivae in rabbits was observed and photographed during life. In the microscopic sections, edema was regularly noted and was frequently accompanied by inflammation, not only in the eyelids and conjunctivae, but also in the extraocular muscles, the connective tissues, and in the choroid. The experimental findings indicate that in addition to the extraocular muscles, the other ocular structures may be expected frequently to show pathologic changes in severe trichinosis.

DISCUSSION

HAROLD W. BROWN: As Dr. Gould has pointed out, this is one of the most important public health parasitic diseases. He mentioned that approximately 25 per cent of us are going to have this before we go to our graves. In New Orleans they found 3.5 per cent of the population were infected, which indicates something of the way in which the southerners cook their meat. In Rochester, New York, 17.5 per cent were found to harbor the infection at autopsy, and in Boston 27.6 per cent; in New York we recently had eighty-four cases which came not from poorly cooked pork chops, but the wursts, and here in New York this is due largely to the people from

Central Europe who eat prepared wursts and sausages which they do not ordinarily cook at home. What is the chance of getting infected meat? In Philadelphia, Dickman[3] found 1.6 per cent of the pork chops were infected; if you ate sausage, 9.5 per cent were infected. Schwartz[4] found the Trichinella cysts in 1.0 per cent of 1,118 frankfurters examined. You will see that we have here a real problem in public health. You as ophthalmologists, can diagnose it, but we have several other techniques which will help to confirm the diagnosis early in the disease. We have an intracutaneous test that is probably 90 per cent accurate. It becomes positive about the fourteenth day, and if you get a positive test on the fifteenth or sixteenth day, that is significant. We do not wait for the fourteenth day, because a negative test followed later by a positive test is most significant. The New York City Health Department will do a complement fixation test and a flocculation test, and here again we do them immediately on suspecting the diagnosis, because a negative test turning to positive is very suggestive.

As far as treatment is concerned, we have no specific chemotherapy, only supportive treatment. A number of years ago a piperazine compound was used, and it looked as though it might have been of some value. We have been trying out a large number of piperazines on infected mice and eventually one of them may prove to be of some value, but you can see from Dr. Gould's slides it is very difficult to get at the adult worm which is embedded in the intestinal mucosa. That is our real problem.

As far as control is concerned, the facts are really very simple. From the individual's standpoint, all one has to do is to cook his pork and cook it thoroughly. If one eats sausage or wurst as they are obtained from the butcher, theoretically they are supposed to have been processed to kill the larvae, but practically this has not always been done. The real control consists of controlling the infection in hogs, and the way to do that is to cook the garbage fed to hogs; some forty-one States have such a regulation, because it is through eating this 1.6 per cent pork chops and 9.5 per cent sausage scraps that the disease is spread from one hog to another. We know the diagnosis; we have no specific treatment, and what we have to depend on is individual control through cooking and mass control through the cooking of garbage, although recently I noticed that Dr. Gould[5] has a paper out suggesting the protection of pork through certain irradiative processes which may be the final solution.

EDWARD BASSEN: Dr. Gould, it has been a great pleasure to listen to your presentation of what I would call a fascinating and intriguing subject. If a million people become infected with trichinae yearly, and if in those patients who develop symptoms the eye symptoms are the most prominent in 45 per cent of the cases, I suppose it behooves us to be on the lookout for this disease. I should like to present three cases which Dr. Perera and I have seen within recent years in our office. I see Dr. Meek in the audience; I am sure he and others of you who were at the New York Eye and Ear Infirmary will remember this disease, because it was one of Dr. Verhoeff's favorite diagnoses. He used to amaze us, as young residents, the first, second, or third time, by looking at the characteristic periorbital edema and diagnosing trichinosis. In these cases the blood count would show 40 to 60 per cent eosinophils, and if you have once seen the very characteristic eye picture, for the rest of your life you won't miss the diagnosis. In my medical student days we were still being taught that in a diagnostic problem one should suspect syphilis. I suppose nowadays a medical student never sees a case of syphilis, and I think trichinosis has taken its place as the chameleon of diseases. It can take the form of almost anything. I think if you would buy one of the bottles of patent medicine they used to sell forty or fifty years ago and read the list of diseases which that magic cure-all would take care of, one would find listed there all of the diseases which trichinosis can imitate. The literature on the subject is most varied. It is a moot question in theological schools whether or not the Mosaic proscription of

the eating of pork was related to the ancient Hebrews' actually knowing about trichinae. Three or four years ago our most interesting local magazine, The New Yorker, contained a fascinating article, of all things for the audience of The New Yorker, on trichinosis. That was some time in 1950.

The first case I would like to present was a young man of twenty-five who came to the office complaining of swelling of his lids. He had no pains or aches, was not ill, and he had what I would call the characteristic appearance of periorbital edema. A blood count showed 44 per cent eosinophils, and the man never had another symptom. Three months later he still had 35 or 40 per cent eosinophils; then he disappeared.

The second case is that of a female about thirty-five years of age, a patient of Dr. Perera's. She came in with the characteristic edema which was so marked that she had an actual exophthalmos of one eye. Dr. Perera sent her to her family physician. Her temperature was 103 or 104; she was very ill, and was admitted to the hospital, and on the basis of a 45 per cent eosinophilia, together with the eye picture, the diagnosis of trichinosis was made. She had a very stormy time; she had neurologic and cardiovascular symptoms, with her temperature running to 104; she was on the danger list for two weeks, finally recovered, and is now well.

Dr. Birchell is here tonight, and at dinner he showed me a slide of encysted larvae in the deltoid muscle. Those of you who remember Dr. Ben Witt Key will recall that in 1929[9] he published a case similar to Dr. Perera's. The exophthalmos was so marked that the patient was admitted to the New York Eye and Ear Infirmary with the diagnosis of orbital cellulitis secondary to sinus disease. Surgery was planned, but the x-ray studies proved negative. During the interval a blood smear had been examined, which showed 70 per cent eosinophils. Based on the eye picture and the blood count, surgery was postponed, a tentative diagnosis was made of trichinosis, and three days later a section was taken from the deltoid, which was positive for the larvae. This is the slide in Dr. Birchell's possession.

The third case I should like to present is that of a woman thirty-five years of age who came to the office with what I call the characteristic eye picture, but she also had been feeling ill; she had pains and aches. On the basis of the eye picture I called her family physician and said I thought she had trichinosis, and asked him to examine her and do a blood count. Apparently he had never seen a case of trichinosis, and decided she had the grippe, so he gave her Aureomycin and penicillin and streptomycin for a week; after that, her temperature having gone to 104, he began to question his diagnosis, and did a blood count. She had eosinophils of only 14 per cent. She developed neurologic symptoms, lost the use of her right leg, and was admitted to the City Hospital of New York with the diagnosis of trichinosis. The neurologic picture was so bizarre and confusing that they would not accept the admission diagnosis. They did repeated lumbar punctures and never got the same findings twice. It was a confusing, non-definitive picture, and after she had been very sick for two weeks they biopsied the deltoid muscle, which showed the larvae. She was acutely ill for six weeks. The last time I saw her she was well and very happy because her case was published and she had a reprint to show about her illness. But she is unhappy about another thing, because she has to forego a weekly pleasure which she had previously enjoyed of a meal at a Chinese restaurant, where she would eat pork chops and spareribs. Now she is afraid of getting trichinosis again, and she has had to give up that little pleasure.

ALFRED ANGRIST: Dr. Gould, in closing will you comment on our experience in a survey we did in our institution where we found about 30 per cent of the population showed trichinae in larval form in the diaphragm, and the highest percentage was in patients who should have obeyed the Mosaic Law, but apparently had not?

S. E. GOULD: The only reference I can give to the last comment of Dr. Angrist regarding the incidence of trichinosis in Jewish patients is the survey made by the

U. S. Public Health Service which was done with the cooperation of a great many hospitals throughout the country. In this survey covering more than 5,000 autopsies, the average incidence of trichinosis was 16 per cent, but of the patients known to be Jewish, the incidence of trichinosis was only 1 per cent. In a clinical study on 3,000 hospital patients, we found that 6 per cent gave an immediate skin reaction with a trichina antigen, while among 100 inmates in the Jewish Old Folks Home in Detroit, we found that only 1 gave an immediate positive skin test.

Concerning the value of the skin test, we conducted a clinicopathologic study in which we compared the skin tests during life with the finding of Trichinella spiralis in the same persons in 388 autopsies. Only 10 per cent of those found to be harboring larvae in their muscles had given a positive skin test during life, while 5 per cent of those in whom no larvae were found at autopsy had given a positive test during life. Consequently, the test has little value in indicating the presence or absence of old trichinosis. It is believed, however, that the immediate skin test is frequently of diagnostic value in recent trichinosis, but that after a few years the skin loses its reactivity.

One word about treatment. The only drugs that might be given with benefit are ACTH and cortisone. Either of these should lessen the severity of the symptoms, and may have a favorable effect on the course of the disease itself, during its acute stage. If the severity of symptoms can be eased, a good deal will be accomplished for the comfort of the patient and perhaps also for the outcome of the disease. After a day or two of treatment the aches and pains may subside, and the patient may believe that he is on the road to recovery. However, if the medicament is discontinued, the pains may return in all their severity and the patient then knows that he is not yet well, and should remain under treatment. In severe infections it is important to confine the patient to bed until all danger from myocarditis has passed. The heart symptoms are likely to appear one or two weeks after the muscle symptoms begin to subside, and therein lies the danger of permitting the patient out of bed too soon. In moderately severe cases, therefore, it is well to keep the patient in bed and take electrocardiograms at different times. We had a case in point. One of our supervising nurses entered the hospital after an illness of four weeks. The diagnosis was made on finding an eosinophilia of 62 per cent. We put her to bed at absolute rest, under the care of nurses, day and night. She said it was silly to give her so much attention, and that she was not that sick. Ten days after she had been put on absolute bed rest she developed palpitation, smothering sensations over the precordium and significant electrocardiographic changes that had not been present previously. These symptoms and electrocardiographic changes persisted for ten days, after which she recovered. Many a patient has died suddenly from heart failure after having been allowed to get out of bed, after the muscle symptoms had begun to abate, in the belief that he was on the road to recovery.

I might conclude with a story told about Virchow, who helped work out the life cycle of the parasite. It happened that Virchow was also a leader of the Reichstag at one time, and that he incurred the displeasure of Bismarck, the Chancellor. Bismarck challenged him to a duel, and Virchow replied: "Inasmuch as I am the one who is challenged, I presume I have the choice of weapons. My weapons are two sausages, one of which contains the deadly trichinae. You may eat the one of your choice." But Bismarck declined.

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TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street, New York

INFECTIONS AND THEIR MANAGEMENT

OCTOBER 18–29, 1954

EVENING LECTURE PROGRAM

MONDAY, OCTOBER 18

PRESIDENTIAL ADDRESS
ALEXANDER T. MARTIN

METABOLIC DETERMINANTS OF INFECTION

Ludwig Kast Lecture

RENE J. DUBOS, Professor of Pathology and Bacteriology, Rockefeller Institute for Medical Research

CURRENT METHODS IN THE TREATMENT OF TUBERCULOSIS

Harlow Brooks Lecture

J. BURNS AMBERSON, Professor of Medicine, College of Physicians and Surgeons, Columbia University

TUESDAY, OCTOBER 19

ALTERATIONS IN PATHOLOGY IN INFECTIONS SINCE THE INTRODUCTION OF CHEMOTHERAPY AND ANTIBIOTICS

Wesley M. Carpenter Lecture

PAUL R. CANNON, Chairman, Department of Pathology, The University of Chicago, Chicago, Illinois

ACUTE NON-PURULENT MENINGITIS

YALE KNEELAND, JR., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University

WEDNESDAY, OCTOBER 20

EVALUATION OF IMMUNOLOGIC METHODS IN THE CONTROL OF POLIOMYELITIS

THOMAS FRANCIS, JR., Professor and Chairman, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

VIRAL HEPATITIS

RODERICK MURRAY, Assistant Chief, Laboratory of Biologics Control, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland

THURSDAY, OCTOBER 21

THE ROLE OF A NEW GROUP OF PREVALENT VIRUSES IN UNDIFFERENTIATED RESPIRATORY ILLNESSES

ROBERT J. HUEBNER, Chief, Section on Virus and Rickettsial Diseases, Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland

INTERACTIONS OF HOST, MICROBE AND CHEMOTHERAPEUTIC AGENT

COLIN M. MacLEOD, Professor of Microbiology, New York University College of Medicine

FRIDAY, OCTOBER 22

THE EPIDEMIOLOGY OF HEMOLYTIC STREPTOCOCCAL INFECTIONS

C. H. RAMMELKAMP, Professor of Medicine, Western Reserve University Medical School and Director of Streptococcal Disease Laboratories, Warren Air Force Base, Wyoming

THE USE OF ANTIBIOTICS FOR THE PREVENTION OF RHEUMATIC FEVER

GENE H. STOLLERMAN, Medical Director, Irvington House; Instructor in Medicine, New York University College of Medicine

(Program continued on following pages)

MONDAY, OCTOBER 25

CURRENT STATUS OF THE DEVELOPMENT OF ANTIMICROBIAL AGENTS
GLADYS L. HOBBY, Ph.D., Research Division, Chas. Pfizer & Co., Inc.

THE COMPLICATIONS OF ANTIBIOTIC THERAPY
LOUIS WEINSTEIN, Associate Professor of Medicine, Boston University School of Medicine and Lecturer on Infectious Diseases, Harvard Medical School

TUESDAY, OCTOBER 26

HORMONES AND INFECTION
LEWIS H. THOMAS, Professor of Pediatrics and Medicine, The Pediatric Research Laboratories of the Heart Hospital, University of Minnesota Medical School, Minneapolis, Minnesota

STAPHYLOCOCCUS INFECTIONS
VERNON KNIGHT, Associate Professor of Medicine, Vanderbilt University Medical School, Nashville, Tennessee

WEDNESDAY, OCTOBER 27

LOW RESISTANCE TO INFECTIONS: RELATIONSHIP TO ABNORMALITIES IN GAMMA GLOBULIN
DAVID GITLIN, Instructor in Pediatrics, Harvard Medical School

PRESENT DAY CONSIDERATIONS OF THE RABIES PROBLEM
HORACE L. HODES, Director, Department of Pediatrics, The Mount Sinai Hospital; Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University

HISTOPLASMOSIS
C. W. EMMONS, Ph.D., Mycologist, National Microbiological Institute, U.S. Public Health Service; Professorial Lecturer, George Washington University Medical School, Washington, D.C.

THURSDAY, OCTOBER 28

THE ACUTE DIARRHEAL DISEASES OF BACTERIAL ORIGIN
F. S. CHEEVER, Professor of Microbiology, Graduate School of Public Health, University of Pittsburgh

EVALUATION OF DIAGNOSTIC TESTS IN INFECTION
CALDERON HOWE, Associate in Microbiology, College of Physicians and Surgeons, Columbia University

FRIDAY, OCTOBER 29

APPROACHES TO THE CHEMOTHERAPY OF VIRAL INFECTIONS
FRANK L. HORSFALL, JR., Member, Rockefeller Institute for Medical Research

ANTIBIOTIC THERAPY OF VIRAL AND RICKETTSIAL DISEASES
JOSEPH E. SMADEL, Director, Division of Communicable Diseases, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C.

REGISTRATION FEES — NON-FELLOWS

Fellows of The New York Academy of Medicine will be furnished registration cards without application and without fee. A registration card will be sent to Non-Fellows upon receipt of check, payable to *The New York Academy of Medicine*, for $10.00 for the entire program, $6.00 for *either the first or second week.*

Medical Officers of the Armed Services, in uniform, will be admitted without charge.

Interns and Residents will be admitted without charge, provided they present letters from their Chiefs of Service. They will be seated as facilities permit, after Fellows of the Academy and other registrants have been accommodated.

(Program continued on following pages)

TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

MORNING PANEL PROGRAM

11:00 A.M. at the Academy

First Week

Monday, October 18

FEVER OF UNDETERMINED ORIGIN

Chairman: Hamilton Southworth

Members: J. Burns Amberson
Joseph H. Burchenal
Yale Kneeland, Jr.
Currier McEwen

Wednesday, October 20

LOCAL USE OF ANTIBIOTICS AND PROTEOLYTIC ENZYMES IN SURGICAL INFECTIONS

Chairman: Louis M. Rousselot

Members: William A. Altemeier
Edward L. Howes
W. Ross McCarty

Friday, October 22

MANAGEMENT OF NON-TUBERCULAR PULMONARY INFECTIONS

Chairman: Dickinson W. Richards

Members: Alvan L. Barach
Perrin H. Long
William S. Tillett

Second Week

Monday, October 25

THE MANAGEMENT OF REGIONAL INFECTIONS

Chairman: Yale Kneeland, Jr.

Members: David V. Habif
John K. Lattimer
Carl T. Nelson
Louis Weinstein

Wednesday, October 27

COMBINED MEDICAL AND SURGICAL TREATMENT OF TUBERCULOSIS

Chairman: Walsh McDermott

Members: Aaron D. Chaves
James G. Hirsch
Herbert C. Maier
Carl Muschenheim
Robert Yeager

Friday, October 29

THERAPY OF AMEBIASIS AND OTHER PARASITIC INFECTIONS

Chairman: Harry Most

Members: Harold W. Brown
B. H. Kean
Elmer H. Loughlin
Howard B. Shookhoff

TWENTY-SEVENTH ANNUAL GRADUATE FORTNIGHT

HOSPITAL CLINICS PROGRAM

CALENDAR OF CLINICS

All Clinics will be held from 2 to 5 P.M.

First Week

Monday, October 18	1. Flower-Fifth Avenue *Hospital Representative:* DAVID LEHR
Tuesday, October 19	2. Mount Sinai *Hospital Representative:* SOLOMON SILVER
Wednesday, October 20	3. Veterans Administration (Bronx) *Hospital Representative:* JULIUS WOLF
Thursday, October 21	4. Presbyterian *Hospital Representative:* HARRY M. ROSE
	5. Polyclinic Hospital *Hospital Representative:* JAMES P. CROCE
Friday, October 22	6. St. Vincent's *Hospital Representative:* C. G. DE GUTIERREZ-MAHONEY

Second Week

Monday, October 25	7. Bellevue *Hospital Representative:* ALPHONSE TIMPANELLI
Tuesday, October 26	8. Willard Parker* *Hospital Representative:* JEROME L. KOHN
Wednesday, October 27	9. New York *Hospital Representative:* RALPH TOMPSETT
Thursday, October 28	10. St. Luke's-Woman's *Hospital Representative:* CHARLES G. ADSIT, JR.
Friday, October 29	11. Lenox Hill *Hospital Representative:* ARTHUR F. ANDERSON

* This clinic *only*, will be held at the Academy; all others at the designated hospitals.

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As in past years, a comprehensive Scientific Exhibit will be an integral part of the 1954 Fortnight.

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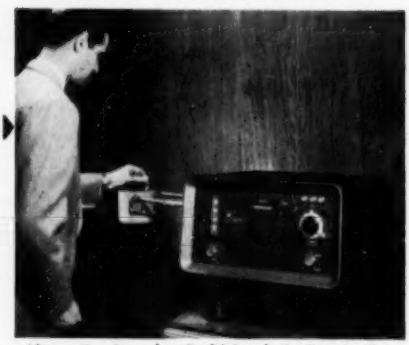

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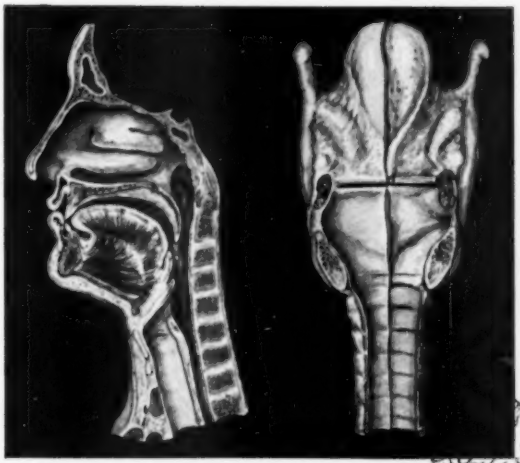
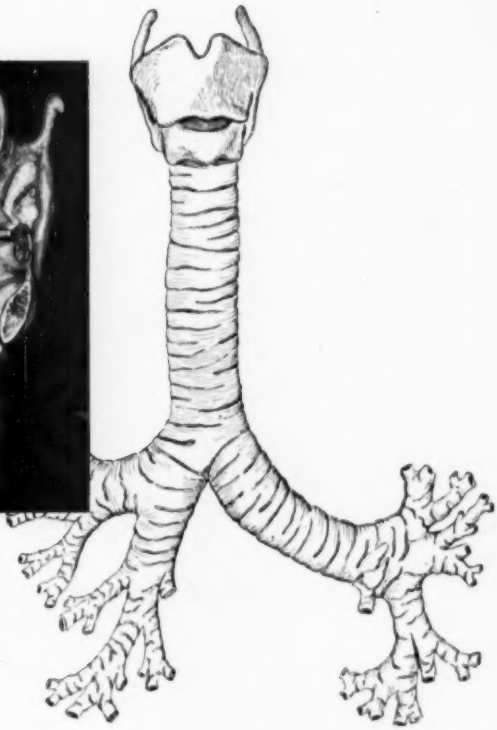
*Maximum time involved—2 minutes.





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IV. RECOMMENDED DOSAGE:

a. *Adults:* one or two Hyadrine tablets three or four times daily, depending upon individual requirements.

b. *Children:* 50 to 100 pounds, one-half to one tablet every four hours; for children under 50 pounds reduce dosage accordingly.

V. PRECAUTIONS:

a. Some few patients may experience drowsiness from diphenydramine in spite of stimulation from Aminophyllin and racephedrine. They should be warned against driving automobiles and similar pursuits.

b. Because of its racephedrine hydrochloride content, Hyadrine should be used with caution in patients with hypertension, organic heart disease, thyrotoxicosis or diabetes mellitus.

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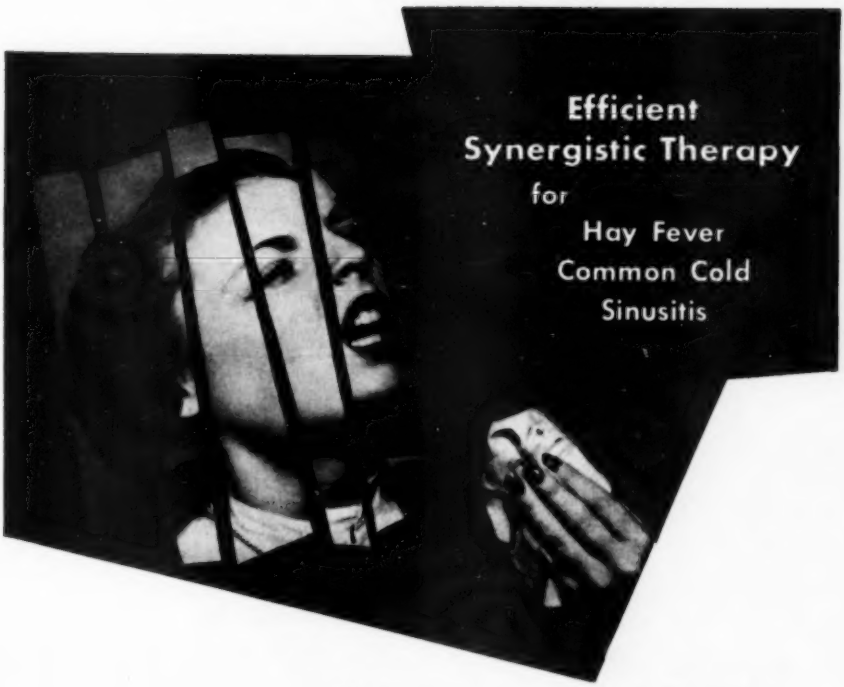

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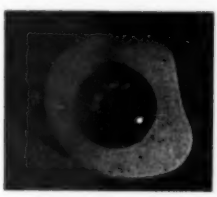

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1. McHardy and Browne: Sou. Med. J. 45:1136, 1952. 2. Lorber and Shay: Fed. Proc. 12:90, 1952.

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